AL-TR-1991-0104

AD-A248 752

COMPARATIVE EFFECTS OF ANTIHISTAMINES ON AIRCREW PERFORMANCE OF SIMPLE AND COMPLEX TASKS UNDER SUSTAINED OPERATIONS

ARMSTRONG LABORATORY

Thomas [illegible]

KRUG [illegible]
San Antonio D[illegible]
[illegible]
San Antonio, TX 7[illegible]

Samuel [illegible]

CREW SYSTEMS DIRECTORATE
Brooks Air Force Base, TX 78235-5000

Douglas [illegible]

[illegible]
4130 Linden Avenue [illegible]
Dayton, O[illegible]

[illegible]

CREW SYSTEMS DIRECTORATE
Brooks Air Force Base, TX 78235-5000

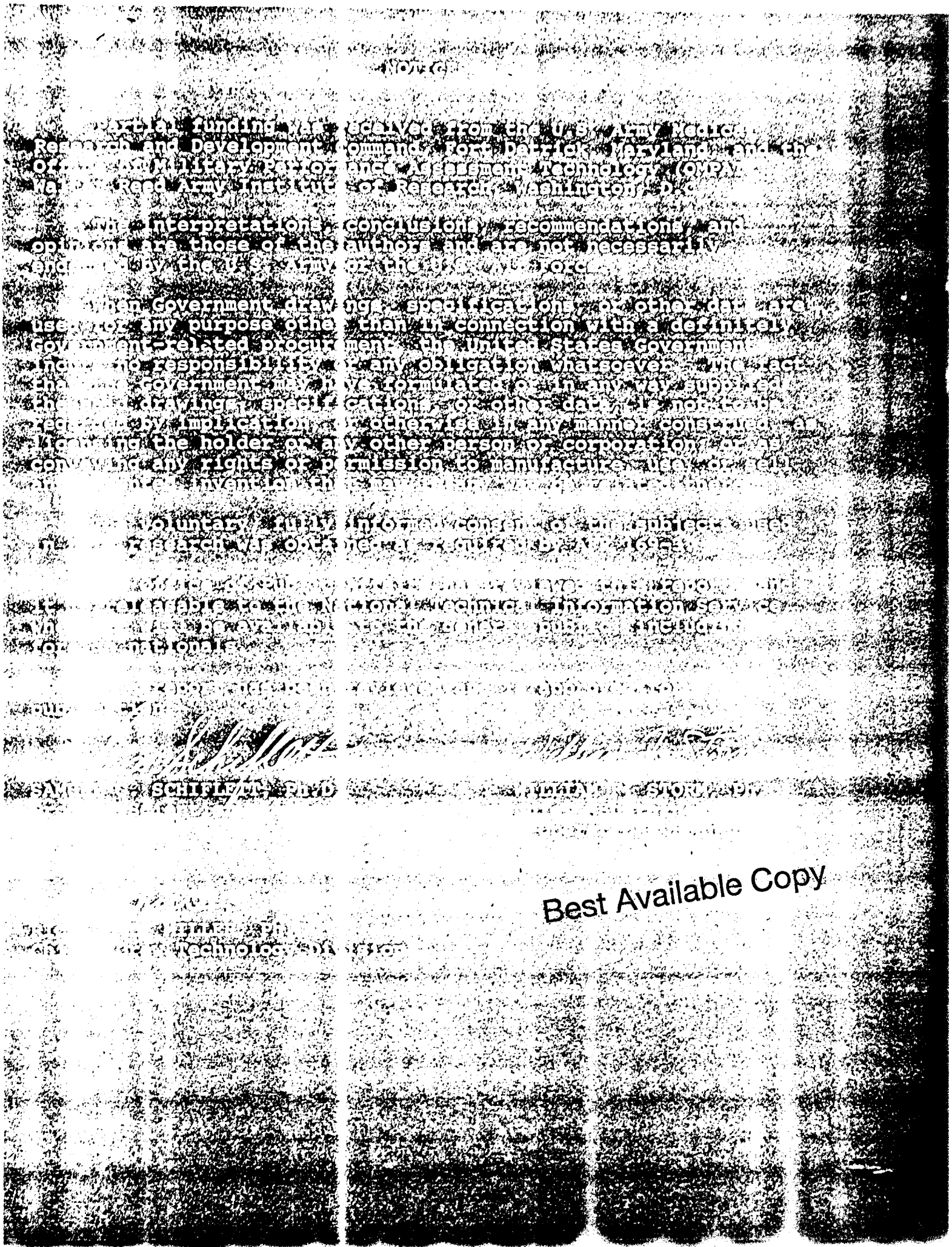
[illegible]

Approved for public release; distribution is unlimited.

92-09801

HEADQUARTERS
US ARMY MEDICAL R&D COMMAND
Fort Detrick, MD 21701-5012

AIR FORCE SYSTEMS COMMAND
BROOKS AIR FORCE BASE, TEXAS 78235-5000



Best Available Copy

REPORT DOCUMENTATION PAGE

Form Approved
OMB No. 0704-0188

1. AGENCY USE ONLY (Leave blank)	2. REPORT DATE	3. REPORT TYPE AND DATES COVERED
	December 1991	Interim Jul 89 - Jul 91

4. TITLE AND SUBTITLE
Comparative Effects of Antihistamines on Aircrew Performance of Simple and Complex Tasks Under Sustained Operations

5. FUNDING NUMBERS
C - F33615-89-C-0603
PE - 62202F
PR - 7930
TA - 19
WU - 07

6. AUTHOR(S)
Thomas E. Nesthus, Samuel G. Schiflett, Douglas R. Eddy, and Jeffrey N. Whitmore

7. PERFORMING ORGANIZATION NAME(S) AND ADDRESS(ES)
KRUG Life Sciences
San Antonio Division
P.O. Box 790644
San Antonio, TX 78216

8. PERFORMING ORGANIZATION REPORT NUMBER

9. SPONSORING / MONITORING AGENCY NAME(S) AND ADDRESS(ES)
US Army Medical R&D Command
HQ USAMRDC SGRD-PLE
Fort Detrick, MD 21701-5012

Armstrong Laboratory
Crew Systems Directorate
Brooks Air Force Base, TX
78235-5000

10. SPONSORING / MONITORING AGENCY REPORT NUMBER
AL-TR-1991-0104

11. SUPPLEMENTARY NOTES
Armstrong Laboratory Technical Monitor: Dr. Samuel G. Schiflett, (512) 536-3464

12a. DISTRIBUTION / AVAILABILITY STATEMENT
Approved for public release; distribution is unlimited.

12b. DISTRIBUTION CODE

13. ABSTRACT *(Maximum 200 words)*
Airborne Warning and Control System (AWACS) Weapons Director (WD) cognitive and psychomotor skills were evaluated with terfenadine (Seldane) and diphenhydramine (Benadryl) using a performance assessment battery (PAB). After nondrug Day 1 training, twelve 3 member teams were tested with Placebo on Day 2, then randomly assigned to Seldane (60 mg/12h TID), Benadryl (25 mg/4h QID), or Placebo groups on Days 3 and 4. An 8-test PAB was given at 1230 and 1330 each testing day. The Seldane and Placebo groups did not differ appreciably from each other on Days 3 or 4, but differed significantly from the Benadryl group. The group showed degraded performance for 7 variables on Day 3 and for 3 variables on Day 4 compared to the Seldane and/or Placebo groups. Subjective measures of fatigue and antihistamine symptoms supported the Day 3 Benadryl impairment. Overall results were consistent with previous research demonstrating cognitive and psychomotor task impairment with Benadryl but not with Seldane. Support for awarding medical flying waivers to non-pilot aircrew who are taking Seldane under the supervision of flight surgeons is offered.

14. SUBJECT TERMS	15. NUMBER OF PAGES
aircrew performance, antihistamines, sustained operations, cognitive and psychomotor performance assessment batteries	40
	16. PRICE CODE

17. SECURITY CLASSIFICATION OF REPORT	18. SECURITY CLASSIFICATION OF THIS PAGE	19. SECURITY CLASSIFICATION OF ABSTRACT	20. LIMITATION OF ABSTRACT
Unclassified	Unclassified	Unclassified	UL

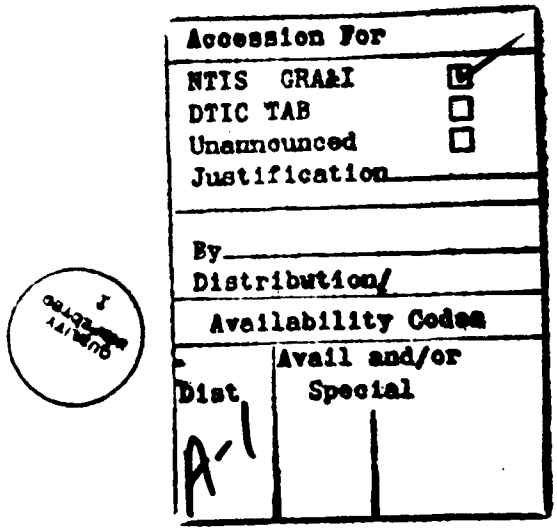
TABLE OF CONTENTS

TABLES

FIGURES

ACKNOWLEDGMENTS

We gratefully acknowledge the assistance of Merrell Dow Pharmaceuticals, Inc. for contributing the Benadryl and Seldane antihistamines and corresponding placebo capsules used in the study. We thank Patricia A. Boll (AL/CFTO) for establishing and maintaining our communication with Merrell Dow. We also wish to acknowledge the assistance of Carolyn J. Oakley (AL/CFTO) for managing the antihistamine and placebo capsule packets for dispensing to the subjects. Last, we wish to thank Carolyn Oakley and Joseph R. Fischer, Jr. (AL/CFTO) for their unhesitating willingness to discuss the data analysis.



COMPARATIVE EFFECTS OF ANTIHISTAMINES ON AIRCREW PERFORMANCE OF SIMPLE AND COMPLEX TASKS UNDER SUSTAINED OPERATIONS

INTRODUCTION

The triservice Office of Military Performance Assessment Technology (OMPAT--formerly the Joint Working Group of Drug-Dependent Degradation on Military Performance, JWGD[3] MILPERF) is investigating the impact of certain classes of drugs on aircrew performance of mission-related tasks in stressful environments. One area of interest involves the effects of antihistamines on complex command, control and communications (C^3) decision-making and synthetic cognitive and psychomotor performance during sustained operations.

Because of the drowsiness side effects, U.S. Air Force (USAF) aircrew are grounded by flight surgeons after prescribing centrally-acting antihistamines for seasonal allergies or for nonallergic rhinitis symptoms. Grounding frequently interrupts flying schedules, causes loss of training, and disrupts crew rest schedules for nonsymptomatic crew members, especially during sustained operations. Recently, however, new antihistamines purporting to have no drowsiness side effects have become available to USAF flight surgeons.

Seldane (terfenadine) is a noncentrally-acting, H-1 type antihistamine with nonsedating properties (Boggs, 1987; Sorkin and Heel, 1985). Benadryl (diphenhydramine) is also an H-1 type antihistamine, but often produces a sedative effect due to direct central nervous system (CNS) activation (Spector, 1987). Seldane has shown little or no performance impairment when compared to the significant performance impairments shown with centrally-active antihistamines such as Benadryl (Fink & Irwin, 1979; Clarke & Nicholson, 1978; Nicholson, Smith, & Spencer, 1982; Nicholson & Stone, 1986; Kulshrestha, Gupta, Turner, & Wadsworth, 1978; Betts, Markman, Debenham, Mortiboy & McKevitt, 1984).

All of the studies cited above used simple performance tasks. The impact of the newer terfenadine medication on complex tasks is relatively unknown. Demonstration of an absence of adverse effects on complex and operationally equivalent tasks under the terfenadine condition compared to a condition known to impair performance, such as diphenhydramine, would add to a growing body of evidence supporting medical flying waivers for nonpilot aircrew. This evidence could potentially reduce grounding time experienced by some aircrew members today. It was our goal to assess the effects of Seldane and Benadryl on simple and complex tasks as well as on measures embedded in multiple high fidelity simulation scenarios of air defense missions of the Airborne Warning and Control System (AWACS) under sustained operations.

Six simple, standardized performance tasks were selected from the Unified Triservice Cognitive Performance Assessment Battery (UTC-PAB; Shingledecker, 1984; Englund, Reeves, Shingledecker, Thorne, Wilson, and Hegge, 1985; Perez, Masline, Ramsey, and Urban, 1987). Two complex synthetic performance tasks were selected from the Complex Cognitive Assessment Battery (CCAB) (Samet, Marshall-Mies & Albarian, 1987).

The 8 standardized tests were integrated into a performance assessment battery we called the 8-test PAB to evaluate the two antihistamines against a placebo. Our selection of the 8 individual tasks was made with respect to their potential sensitivity to drugs (Dichotic Listening Task (DLT), Match-to-sample, Memory search of Combined task), fatigue (DLT, Code Substitution, Pattern Comparison, Grammatical Reasoning, Combined task); their potential predictive capacity for training and selection (DLT, Combined task); and their potential correlation to embedded measures configured into the AWACS simulation scenarios (DLT, Mark Numbers, Numbers and Words, Combined task). Correlations of the 8-test PAB scores with the simulation scenario measures were used to provide data to assess the feasibility of predicting complex "real-world" performance from laboratory tasks under the same medications. The predictive analysis is continuing and results are pending. This report is concerned primarily with the UTC-PAB and the CCAB performance measures as well as with subjective measures of assessing the potential performance impairment produced by the antihistamines.

Task performance degradation was anticipated for the Benadryl antihistamine condition compared to the Seldane and placebo conditions. An interaction of drug condition with time (drug by day) was also anticipated when compared with placebo as fatigue entered the picture.

METHODS

Subjects

The 552d Airborne Warning and Control Systems' (AWACS) Wing, Tinker AFB, OK, assigned twelve teams of weapons director (WD) volunteers (three WDs per team) to Brooks AFB in support of this study. Thirty subjects were male and 6 were female. The average age was 26; the range was 23-34. The educational level of all subjects was post-bachelors degree. All subjects were screened for current prescription medication use, history of antihistamine use, and known lactose sensitivity.

Study Design

The first day was a nondrug training day. All subjects were tested with placebo on Day 2. Placebo was administered during the first testing day to provide a baseline for comparing performance equivalence between groups. Accordingly, this

testing day was single-blind; the investigators were aware of the drug condition on this day, the subjects were not. On Days 3 and 4 (in their respective teams) subjects were tested with a randomly assigned drug condition (Seldane, Benadryl, or lactose placebo; see Table 1). Drug group assignment was double-blind. Neither the investigators nor the subjects were aware of the assigned drug condition on Days 3 and 4.

TABLE 1. DRUG ADMINISTRATION SCHEDULE.

Benadryl Group			
Monday:	Training	-	Placebo at 2230
Tuesday:	Day 1	-	Placebo 0630, 1130, 1500, then Benadryl at 2230
Wednesday:	Day 2	-	Benadryl 0630, 1130, 1500, and 2230
Thursday:	Day 3	-	Benadryl 0630, 1130, and 1500
Seldane Group			
Monday:	Training	-	Placebo at 2230
Tuesday:	Day 1	-	Placebo 0630, 1130, 1500, then Seldane at 2230
Wednesday:	Day 2	-	Seldane 0630, 1130, 1500, and 2230
Thursday:	Day 3	-	Seldane 0630, 1130, and 1500
Placebo Group			
Monday:	Training	-	Placebo at 2230
Tuesday:	Day 1	-	Placebo 0630, 1130, 1500, and 2230
Wednesday:	Day 2	-	Placebo 0630, 1130, 1500, and 2230
Thursday:	Day 3	-	Placebo 0630, 1130, and 1500

NOTES: Teams were grouped into different drug conditions; either diphenhydramine (Benadryl), terfenadine (Seldane), or Placebo (lactose). Data collection normally started no sooner than 1 hour after drug administration, except after the 2230 dosage. Subjects consumed no more than eighteen capsules total. Benadryl subjects consumed no more than 100 mg daily and Seldane subjects consumed no more than 120 mg daily.

Apparatus

Testing Room Layout.

Each team of three subjects was tested simultaneously in a room 6.7 x 11 m (22 x 36 ft). Five subject booths containing a computer, monitor, keyboard, and response box were situated along the long wall of the room. Each booth was partitioned on three sides. Subjects could not see one another's work, nor did they attempt to do so. The tests were performed by the subjects in their assigned booths (1, 2, or 3), with the exception of the DLT; it was taken in the left-end booth dedicated solely to the DLT.

The test administrator was seated at a table centered a few feet behind the subject booths. Overhead fluorescent lights illuminated each booth with approximately 100 Lux measured at the eye level of a seated person. The dim illumination approximated that of the AWACS simulation scenario (and operational) environment.

Hardware and Software.

All tests, with the exception of the DLT, were installed on three of four Zenith Z-248 computers. Equipment necessary for the successful use of these tests is specified in Reeves, Thorne, Winter, Hegge (1989). The system included a BASIC interpreter (BASICA.EXE), SRL PC LABPAC card (a multiple-timer plug-in card), a Modulus III response box from Stimulus Equipment Corporation, an audio output filter box from NAMRL, and a set of headphones. Data for the DLT were collected on a separate machine because its program required different dip-switch settings on the LABPAC board making it incompatible with the other test-machines.

Cognitive and Psychomotor Performance Tests

Appendix A briefly describes each of the 8 tests used for assessing cognitive and psychomotor performance. The tests are as follows: **Matching-to-Sample** (A.1.) as specified by the Naval Medical Research Institute (NMRI); **Code Substitution** (A.2.), **Pattern Comparison** (A.3.), and **Logical Reasoning** (A.4.) from Walter Reed Army Institute of Research (WRAIR); **Mark Numbers** (A.5.) and **Numbers and Words** (A.6.) from the Complex Cognitive Assessment Battery (CCAB), Army Research Institute (ARI); **Dual Task** (A.7.) from the USAF School of Aerospace Medicine (USAFSAM); and the **Dichotic Listening** (A.8.) from the Naval Aerospace Medical Research Laboratory (NAMRL).

Each test was programmed to operate within the constraints and specifications defined in Perez, Masline, Ramsey, and Urban (1987), and more specifically in Thomas and Schrot (1988) for NMRI-PAB; Thorne, Genser, Sing, and Hegge (1985) for WRPAB; Samet, Marshall-Mies & Albarian (1987) for CCAB; Systems Research Laboratories (1987) for the combined task implemented on the Performance Evaluation Device (PED); and Reeves, Thorne, Winter, and Hegge (1989) for NAMRL-DLT.

Test completion times were approximate since subjects worked independently at their own speed. However, the average duration of the battery was approximately 50 minutes. The 8-test battery was administered during two test sessions, on each of three testing days, beginning at 1230 and 1330 between the early morning and late afternoon C^3 simulation scenarios. Table 2 shows the daily schedule of testing activities.

Test Order.

Each team member took the series of tests (including the DLT) in a unique order determined by subject number and assigned test booth. This sequence remained constant throughout all sessions throughout the week. Further, these three unique test sequences were used with all 12 teams of three subjects each throughout the experiment. The order of administration for the 8 tests, except for the Dichotic Listening Task (DLT), was as follows: Matching to Sample, Code Substitution, Pattern Comparison, Logical Reasoning, Mark Numbers, Numbers and Words, and Dual Task. Since the DLT was installed on a separate computer, it was taken in an alternating order by the three subjects.

Subjective Reports

The subjective measures pertaining to the 8-test PAB evaluation are briefly described and shown in Appendix B. Included are the: MOOD II from the WRPAB (Thorne, Genser, Sing, and Hegge, 1985) completed first thing each morning and last thing each evening (B.1.); an antihistamine side effects symptom questionnaire (developed in-house by KRUG Life Sciences for USAFSAM/VNB) completed after taking each dose of either antihistamine or placebo (B.2.); a USAF sleep survey (USAFSAM Form 154, Sep 76) completed each morning (B.3.); and the USAF Subjective Fatigue Scale (from the Crew Status Survey; AFSC Form 3243, Jun 85) completed before and after each Simulation and before and after the 8-test PAB (B.4.).

Procedure

Teams were randomly assigned to each drug condition resulting in 4 teams (or 12 Ss) per condition. Table 2 shows a drug administration and experimental event schedule for each 18-hr day. Teams were tested in two 3.5-hr AWACS simulation scenarios and two 50-min 8-test PAB sessions each day for three days starting on Tuesday.

Drug Administration.

All groups followed dosage schedules as recommended for both the Benadryl and Seldane antihistamines (Physicians' Desk Reference, 1989). Subjects in the Benadryl group therefore received 25 mg, Q.I.D.; in the Seldane group, subjects received 60 mg, B.I.D. There are physical and visual differences between Benadryl and Seldane, but not between each antihistamine and its placebo look-alike. In order to keep the experiment double-blind, all subjects received two capsules, one, Benadryl or its placebo, and one Seldane or its placebo on Monday evening, Tuesday morning and evening, Wednesday morning and evening, and Thursday morning. Subjects received a single capsule of Benadryl or its placebo for each of the late morning and middle afternoon doses on Tuesday, Wednesday and Thursday.

In summary, all subjects ingested placebos only during the testing schedule for Tuesday. Thereafter, four randomly assigned teams ingested either the recommended therapeutic dosage of Benadryl plus Seldane placebo, Seldane plus Benadryl placebo, or both Seldane and Benadryl placebo preparations starting on Tuesday evening. Total antihistamine/placebo ingestion for each group consisted of either eight 25 mg Benadryl and ten placebo preparations; four 60 mg Seldane and fourteen placebo preparations; or eighteen placebo preparations.

TABLE 2. DAILY TESTING SCHEDULE.

Time	Activity
0600	Breakfast & mission planning
0630	Drug/placebo ingestion, questionnaires
0700	AWACS simulation pre-brief
0730	Run AWACS scenario
1100	AWACS simulation post-brief
1130	Lunch, drug/placebo ingestion, questionnaires
1230	8-test PAB (test session 1)
1330	8-test PAB (test session 2)
1430	Mission planning & snack
1500	Drug/placebo ingestion, questionnaires
1530	AWACS simulation pre-brief
1600	Run AWACS scenario
1930	AWACS simulation post-brief
2000	Questionnaires
2030	Supper, free time (see notes)
2230	Drug/placebo ingestion, questionnaires (but not on Thursday)

NOTES: Precautions each evening: Bed early (2230), light dinner. Keep blood alcohol levels to below legal limits (0.1%).

Recommended Breakfast: juice, fruit, toast, water, doughnuts, decaffeinated coffee or soft drinks, herbal tea.

Recommended Lunch: salad, vegetable soup, crackers, cookies, decaffeinated soft drinks, herbal tea, fruit, no chocolate.

Caffeine intake was restricted throughout the testing session. Decaffeinated coffee, sodas, herbal tea, and water were available periodically during the off-task time. Smoking was allowed in designated outside areas during off-task periods only. The subjects ate low-fat, low-protein meals to prevent the slow absorption of drug into tissues due to plasma protein binding.

Training.

Training in the 8-test PAB and the AWACS simulation scenarios took place on Monday for approximately 8 hours. Teams trained on six simple computerized tests and two complex tests over two 2-hr blocks; one in the morning and one in the afternoon. They also ran a 3-hr C^3 simulation training scenario during the middle of the day to familiarize themselves with the simulated AWACS crewstations and scenarios.

No drugs were administered during the training sessions on Monday. Before retiring on Monday at 2230, and again on Tuesday at 0600 after a normal breakfast meal, each team member ingested two lactose placebos (see Table 1) to begin the single blind, Day 2-placebo baseline.

Testing.

After arriving at the Aircrew Evaluation Sustained Operations Performance (AESOP) facility, each team member completed a sleep survey, a USAFSAM subjective fatigue rating scale, an antihistamine side effects symptom questionnaire, and a computerized mood survey (MOOD II) from the WRPAB. At 0630 our AWACS Senior Director (SD) presented a normal AWACS briefing of the upcoming simulation scenario (Sim). Next, the team began the first scenario for the day, which was either high- or low-workload, depending on the order of assignment. Following the 3.5-hr Sim a post-briefing was conducted. The WDs ate lunch before ingesting the late morning dosage. At 1230 the teams reported to the performance assessment laboratory and began the first of two 8-test PAB sessions. After completing the first test session and a short break, they began the second test session at 1330. Mission planning for the late afternoon Sim began at 1430 after a light snack; it was followed by ingesting the middle afternoon dosage and completing a questionnaire. The afternoon Sim prebrief was conducted at 1530; the scenario began at 1600. A postbriefing was conducted after completing the afternoon Sim. The MOOD II survey was taken and the team was given instructions concerning the evening drug condition dose and completing the questionnaire. The team was released at around 2000 hrs for the evening.

The single blind placebo baseline continued Q.I.D. throughout Tuesday, the first day of testing (refer to Table 2), until the fourth or evening dose, which began the true antihistamine or placebo conditions. Depending on group assignment, subjects ingested either Seldane (60 mg) plus Benadryl placebo; Benadryl (25 mg) plus Seldane placebo; or both lactose placebos before retiring at 2230 Tuesday.

At 0600 Wednesday, depending on group assignment, each team member ingested the two capsules; the assigned drug condition plus placebo (or two placebos) after the breakfast meal. All events of Tuesday were repeated on Wednesday and Thursday with the exclusion of the 2230 dosage on Thursday.

The only free time available to subjects during the four days was in the evenings when they were instructed to eat light, minimize alcohol intake and retire by 2230. Few subjects had the reserve energy to do much more than eat, take their evening medication, and retire. A medication reminder call was made by the experimenters to each subject at approximately 2200 to insure compliance with the medication regimen.

Statistics

Data collected during the 8-test PAB sessions were evaluated using an analysis of variance (ANOVA) with two repeated measures (day and test session) on one grouping factor (drug group). In the event that group differences were found on Day 2 (the placebo baseline test day), separate delta score analyses would be conducted for Days 3 and 4. Nonparametric and conservative parametric tests were conducted with the mood/survey/symptom questionnaire data. Data reduction and analysis of the simulation scenario and team performance measures were not completed in time to be included in this report. Results of some of the simulation data were reported elsewhere (Eddy, Dalrymple, and Schiflett, pending review). Linear regression techniques are expected to provide results concerning the predictive power of the simple task measures to complex real-world measures under the various drug conditions as the reduced simulation scenario data become available.

RESULTS

Analysis of the 8-test PAB data first involved an assessment of effects across drug, day, and test session for the three test days--Tuesday (placebo baseline day for all subjects), Wednesday, and Thursday (antihistamine or placebo condition days).

Performance Testing

Three-Day Analysis.

Our rationale for conducting the three-day analysis, including the placebo baseline Day-2 data, was to assess group equivalency before the antihistamine conditions began. We anticipated group effects (drug) across Day (i.e., a drug-by-day interaction); and possibly across test session (i.e., a drug-by-day-test session interaction). Differences on Tuesday (Day 2) the placebo baseline day were not expected.

Six measures showed drug-by-day interaction effects and included: correct response time (RT) $F(4,66) = 2.80$, $\mathbf{p} = 0.03$ of the Pattern Comparison test (WRPAB); the composite score $F(4,66) = 2.47$, $\mathbf{p} = 0.05$, the first correct "word" solution measure $F(4,66) = 3.60$, $\mathbf{p} = 0.01$, and RT of the second "word" solution $F(4,66) = 2.69$, $\mathbf{p} = 0.04$ of CCAB's Numbers & Words test;

errors committed during the first alphanumeric string $F(4,66) = 3.48$, $p = 0.01$ of the dichotic listening task (DLT); and boundary hits $F(4,66) = 2.65$, $p = 0.04$ also called control losses which occurred during the tracking portion of PED's dual task.

Duncan's Multiple Range Test of Means, revealed drug group differences on Day 2 in five of six significant measures. Figures 1-6 display the drug-by-day means for each measure. Significant Least Squares (LS) Mean t-Test contrasts are indicated by asterisks in each figure for group differences by day. Two asterisks above or below a drug-condition letter indicates that the drug condition mean is significantly different from either of the remaining drug condition means on that day. An asterisk with a drug-condition letter within parentheses indicates that the drug condition mean is significantly different from the drug condition mean within the parentheses on that day. The Day 2 drug group differences included: correct response time (RT), composite score, first "word" solution, RT of second "word" solution, and boundary hit measures, as can be seen in Figures 1-4, and 6.

Day 2 was our 'single blind' placebo baseline test day where group differences were not anticipated. Because differences did occur, a second (a priori) analysis was conducted to compare groups after adjusting for baseline performance. Delta scores were therefore computed for each subject by subtracting Day 2 performance from Day 3 and Day 4 performances, respectively.

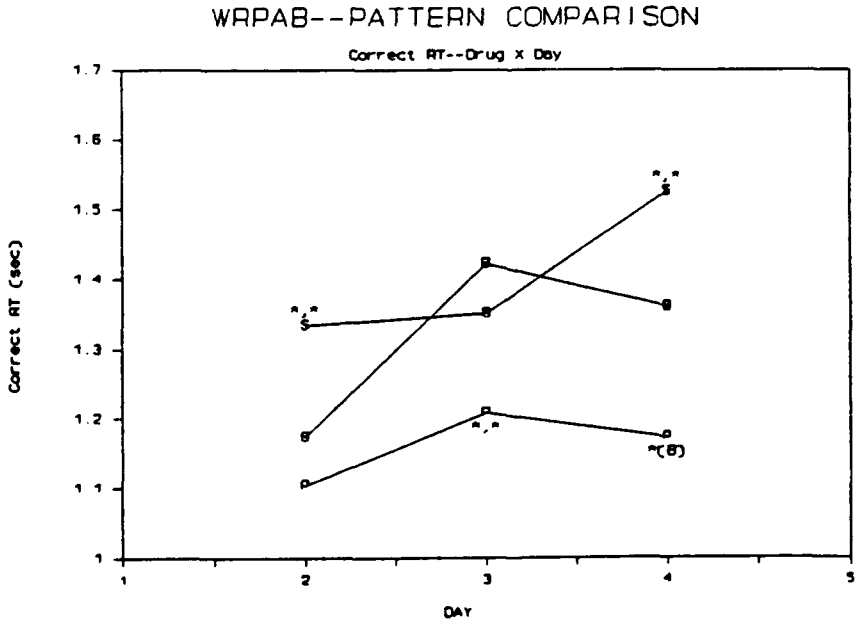


Figure 1. Drug-by-day interaction for Pattern Comparison, RT.

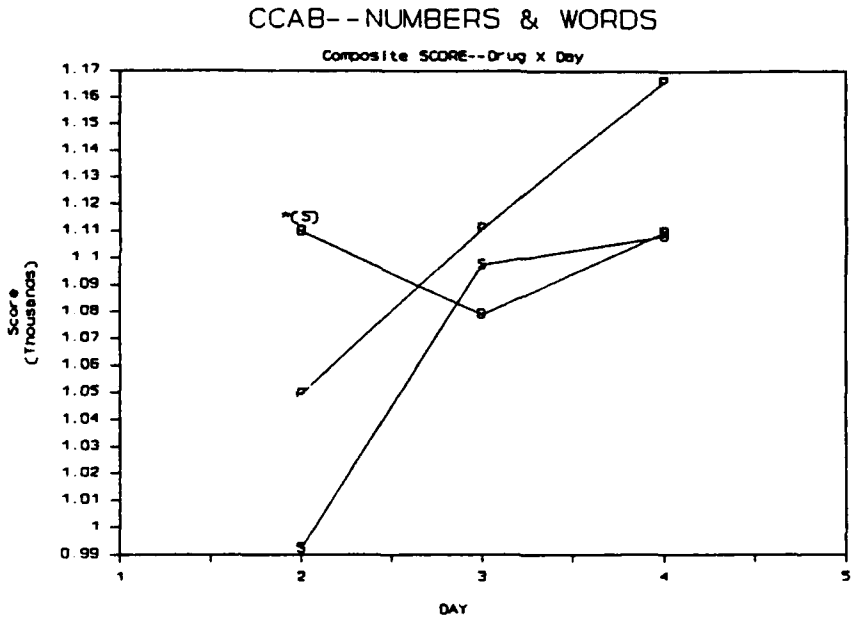


Figure 2. Drug-by-day interaction for Numbers and Words, Score.

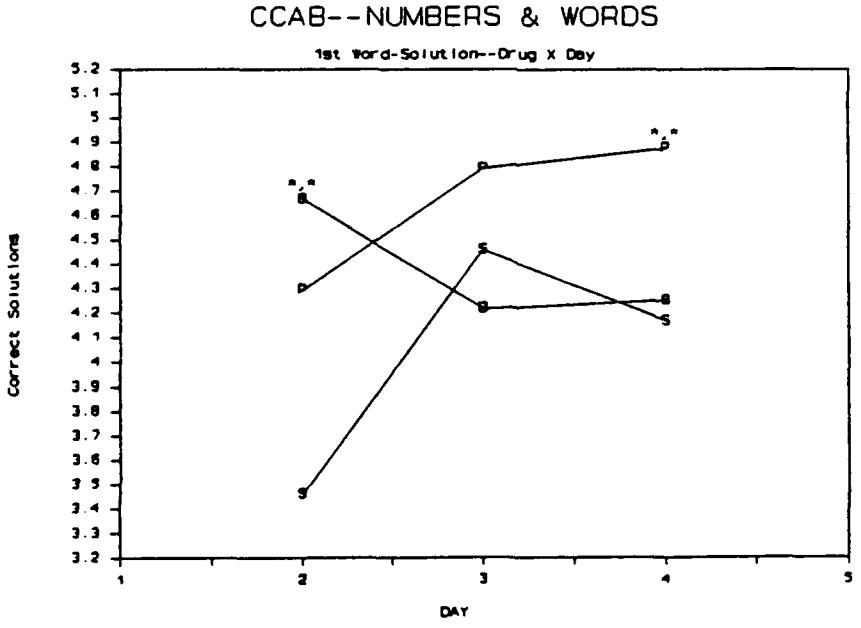


Figure 3. Drug-by-day interaction for Numbers and Words, 1st Solution.

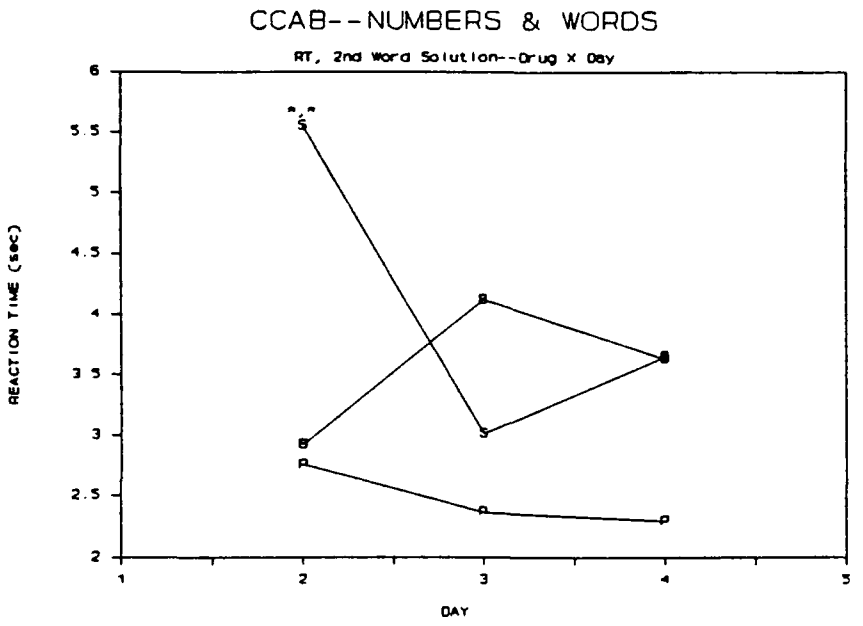


Figure 4. Drug-by-day interaction for Numbers and Words, 2nd Solution RT.

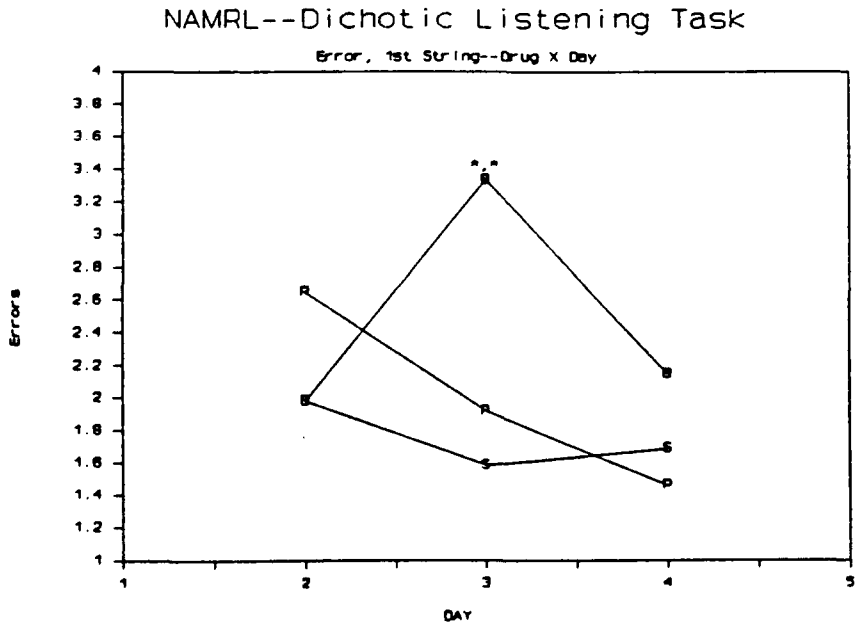


Figure 5. Drug-by-day interaction for Dichotic Listening, Error 1.

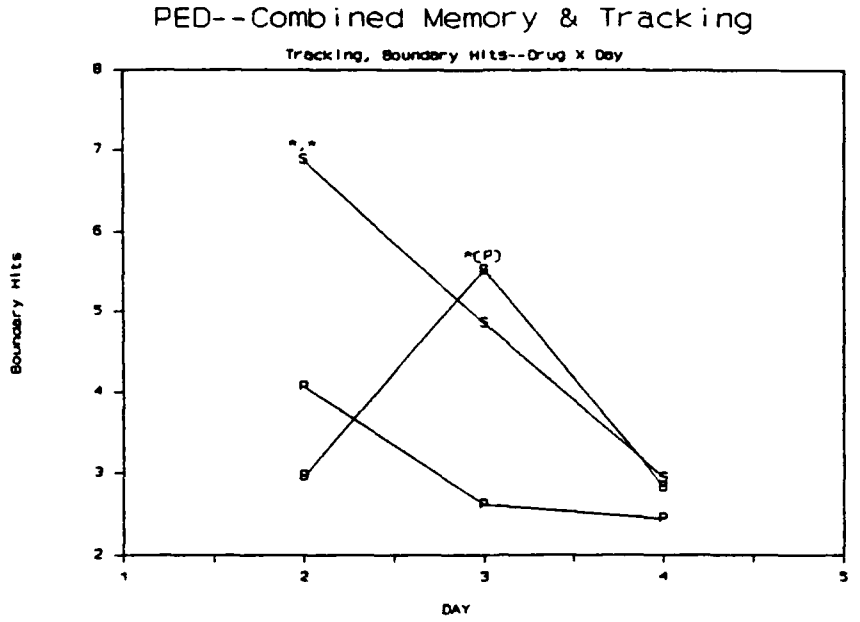


Figure 6. **Drug-by-day interaction for Dual Task, Boundary Hits.**

Day 3 and Day 4, Delta Analysis.

Since the delta score for Day 3 represented a change from Day 2's performance and was analyzed separately from the Day 4 delta score, which also represented the change from Day 2's baseline performance, drug main effects and drug-by-test session interaction effects were now the sources of design interest. Eleven variables showed drug main effects; eight measures were significant on Day 3 and four measures were significant on Day 4. The drug main effects are summarized in Table 3.

Day 3. The significant Day 3, drug main effects involved the following variables: correct RT $F(2,33) = 3.90$, $p = 0.03$ from Pattern Comparison (WRPAB); composite score $F(2,30) = 3.67$, $p = 0.04$ from Mark Numbers (CCAB); composite score $F(2,33) = 5.08$, $p = 0.01$, first "word" solution $F(2,33) = 6.90$, $p < 0.01$, and RT of second "word" solution $F(2,33) = 4.68$, $p = 0.02$ from the Numbers & Words test (CCAB); error of first alphanumeric string $F(2,33) = 5.22$, $p = 0.01$ from DLT; throughput $F(2,33) = 3.66$, $p = 0.04$, and rms-offset $F(2,33) = 3.28$, $p = 0.05$ from the dual task (PED). Seven of the 8 effects showed that for the Benadryl group, performance was degraded compared to Seldane and/or Placebo groups on Day 3. These effects are indicated by asterisks in Figures 7-14.

TABLE 3. DRUG MAIN EFFECT RESULTS OF DELTA SCORE ANALYSES FOR DAYS 3 AND 4

TEST	VARIABLE	DAY 3		DAY 4	
		p	EFFECT	p	EFFECT
Match-To-Sample:					
	MATCH_RT			0.058	P<B
Code Substitution:					
	ERROR			0.04	P>S
Pattern Comparison:					
	CORRECT RT	0.03	B>S		
Logical Reasoning:					
	N.S.				
Mark Numbers:					
	SCORE	0.04	B<S,P		
Numbers & Words:					
	SCORE	0.01	B<S,P		
	SOL1	<0.01	B<S,P	0.04	B<S,P
	RT2	0.02	B>S		
Dichotic Listening:					
	ERROR1	0.01	B>S,P		
PED: DUAL TASK					
	THRUPUT	0.04	S,B<P		
	RMS-OFFSET	0.05	B>P		
	B-HITS			0.055	B>S
	11	8		4	

LEGEND: DR = Drug -- P,B,S = Placebo, Benadryl, Seldane

NOTE: In 7 of 8 variables, the Benadryl group is different from the Seldane, Placebo, or both drug groups on Day 3. In 3 of 4 variables, the Benadryl group is different from the Seldane, Placebo, or both drug groups on Day 4.

Four drug-by-test session effects occurred on Day 3 only. The significant drug-by-test session effects involved the following variables: correct RT $F(2,32) = 6.65$, $p = 0.004$ and the derived throughput measure $F(2,32) = 10.46$, $p = 0.0003$ from Code Substitution (WRPAB); throughput $F(2,31) = 3.40$, $p = 0.05$ from Pattern Comparison (WRPAB); and RT to the first "word" solution $F(2,32) = 6.25$, $p = 0.005$ from Numbers and Words (CCAB). Figures 15-18 show the interaction effects.

Day 4. All Day 4 effects were drug main effects and included: correct match-RT $F(2,32) = 3.12$, $p = 0.058$ from the Match-to-sample test (NMRI); error $F(2,33) = 3.61$, $p = 0.04$ from Code Substitution (WRPAB); first "word" solution $F(2,33) = 3.67$, $p = 0.04$ from Numbers & Words (CCAB); and boundary hits $F(2,33) = 3.18$, $p = 0.055$ from the dual task (PED). Only the error measure from the Code Substitution test (WRPAB) did not show degraded performance on Day 4 for the Benadryl group compared to the Seldane and/or Placebo groups. These effects involved different variables compared to Day 3. The effects are indicated by asterisks in Figures 10 and 19-21.

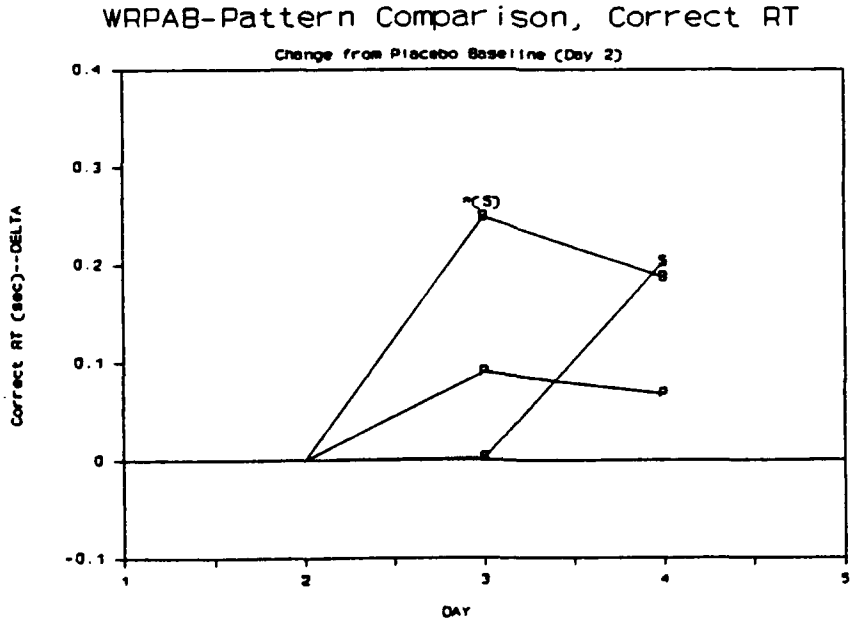


Figure 7. Day 3 delta score drug main effect for Pattern Comparison, RT.

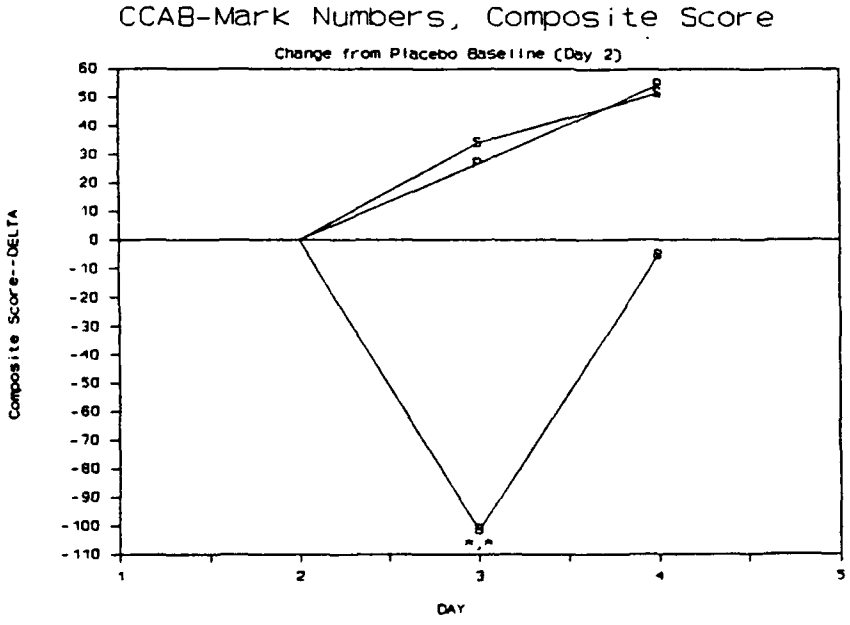


Figure 8. Day 3 delta score drug main effect for Mark Numbers, Score.

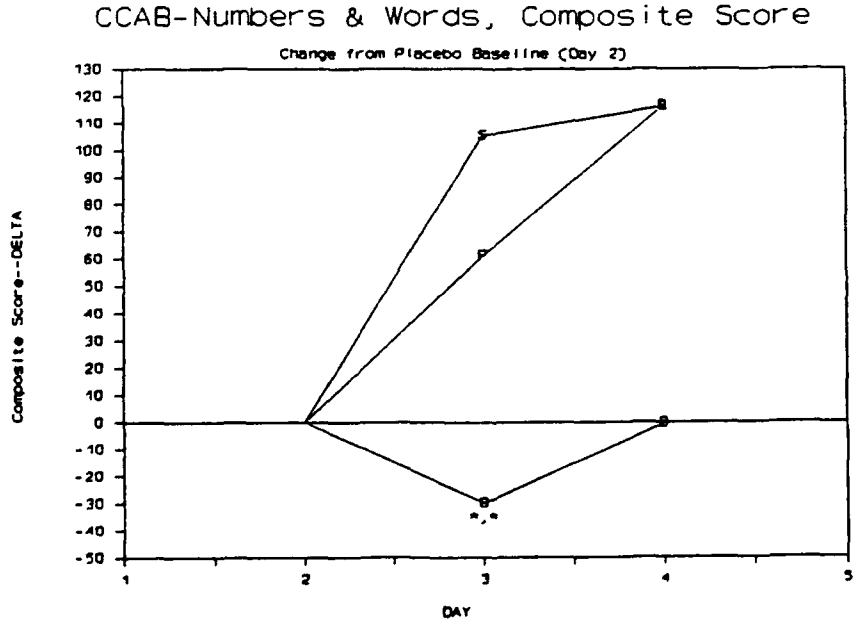


Figure 9. Day 3 delta score drug main effect for Numbers and Words, Score.

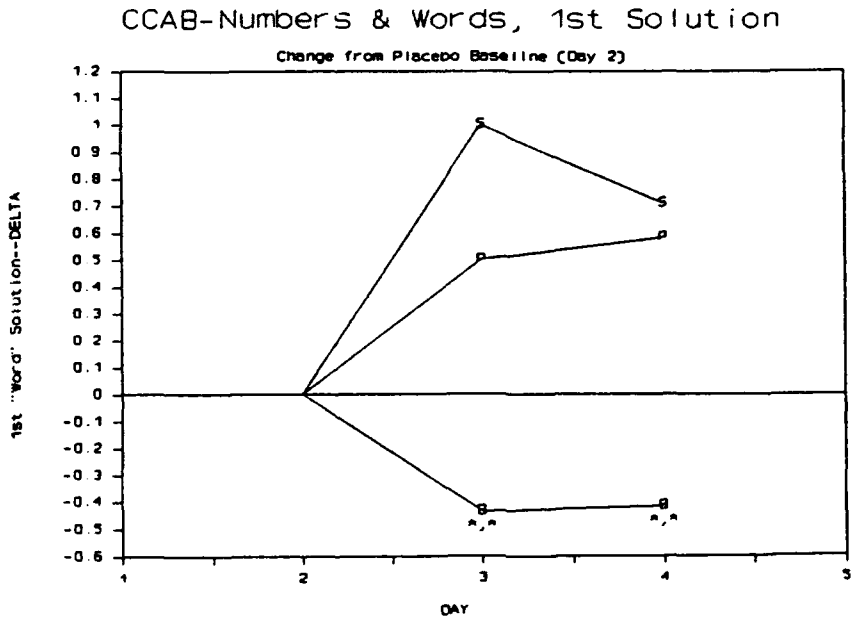


Figure 10. Day 3 delta score drug main effect for Numbers and Words, 1st Solution.

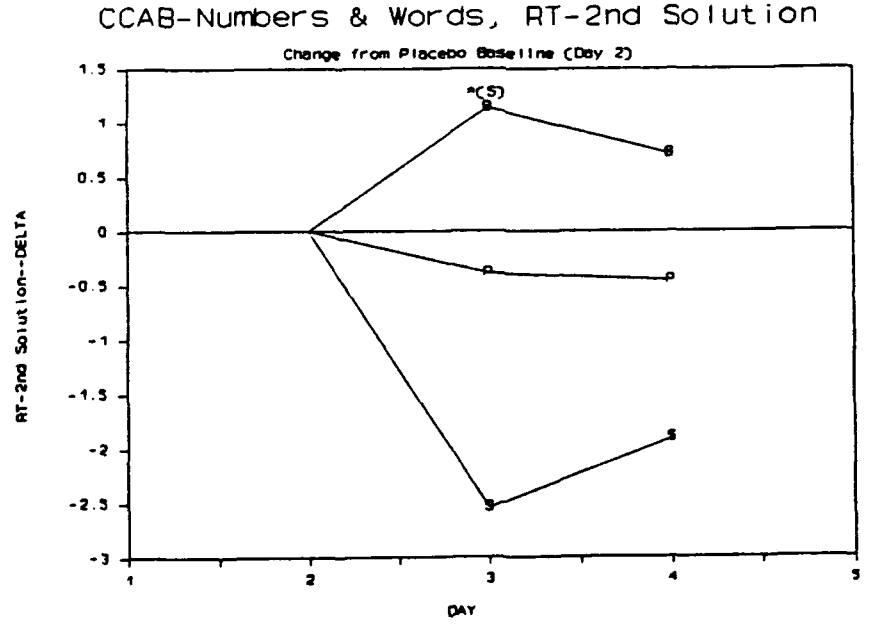


Figure 11. Day 3 delta score drug main effect for Numbers and Words, 2nd Solution RT.

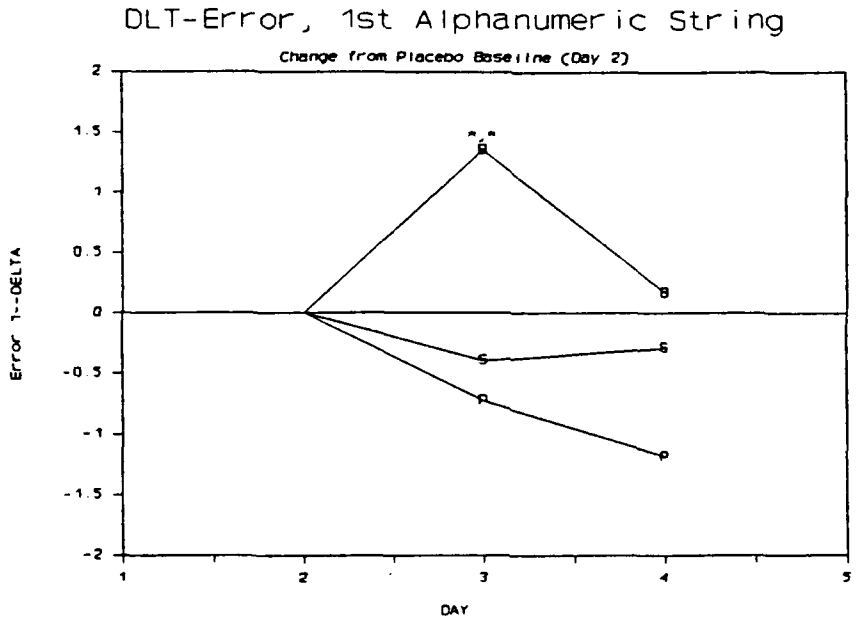


Figure 12. Day 3 delta score drug main effect for Dichotic Listening, Error 1.

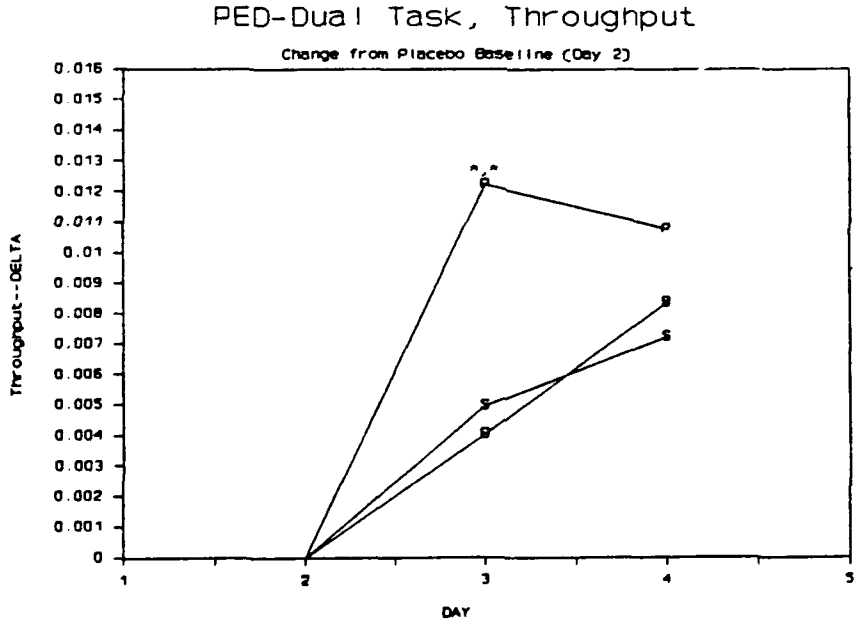


Figure 13. Day 3 delta score drug main effect for Dual Task, Throughput.

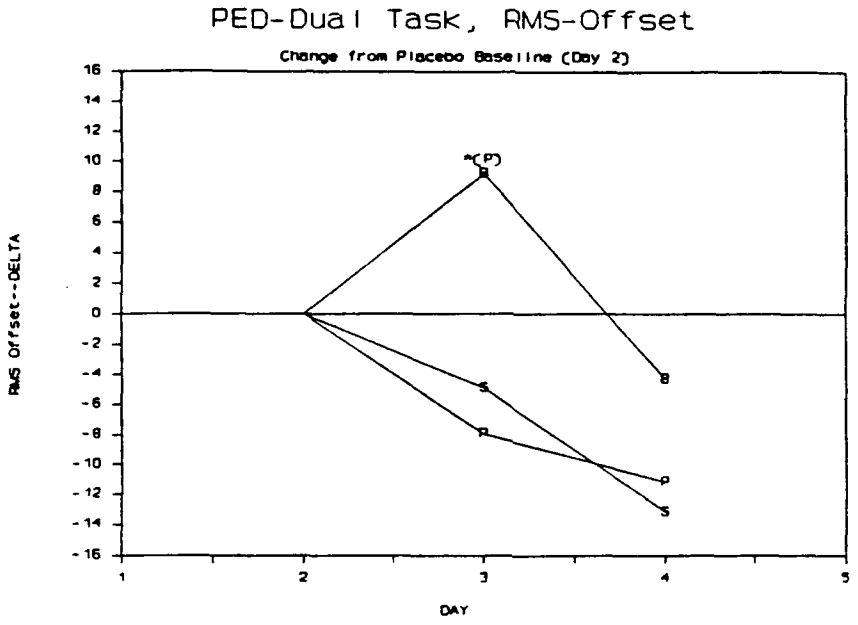


Figure 14. Day 3 delta score drug main effect for Dual Task, RMS Offset.

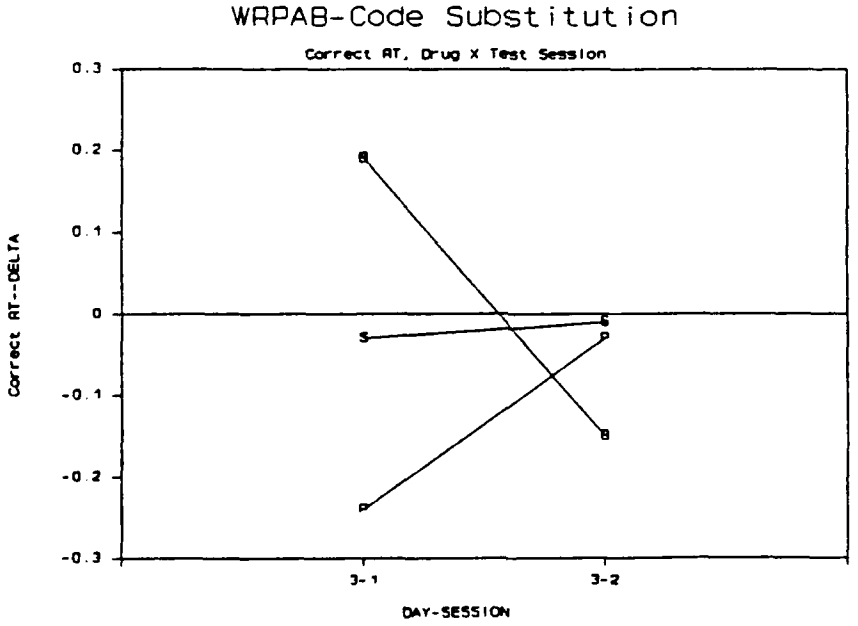


Figure 15. Day 3 delta score drug-by-test session interaction for Code Substitution, RT.

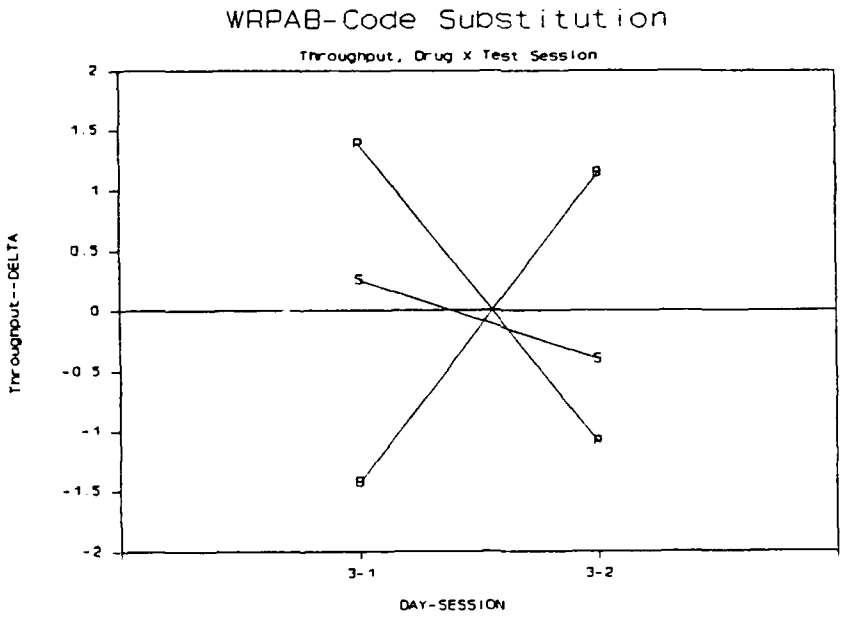


Figure 16. Day 3 delta score drug-by-test session interaction for Code Substitution, Throughput.

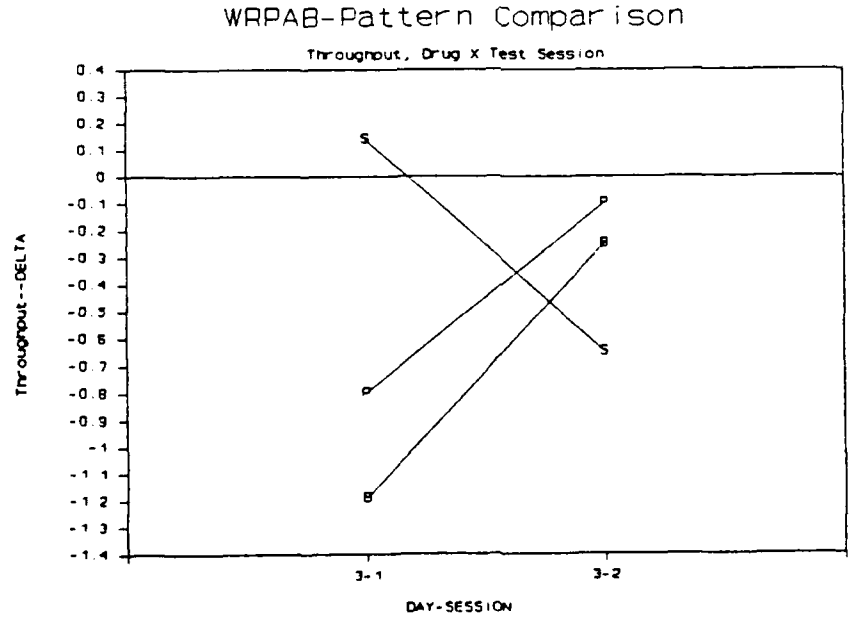


Figure 17. Day 3 delta score drug-by-test session interaction for Pattern Comparison, Throughput.

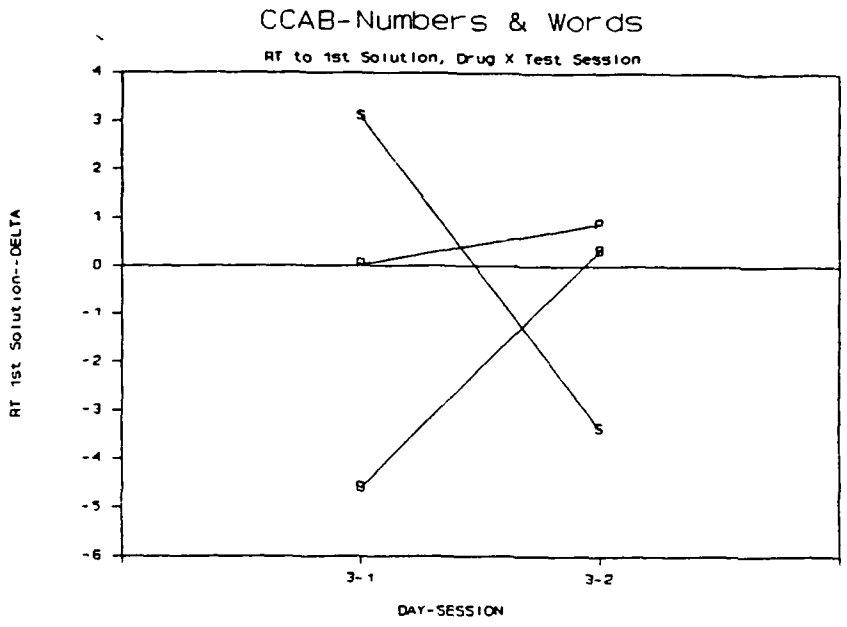


Figure 18. Day 3 delta score drug-by-test session interaction for Numbers and Words, 1st Solution RT.

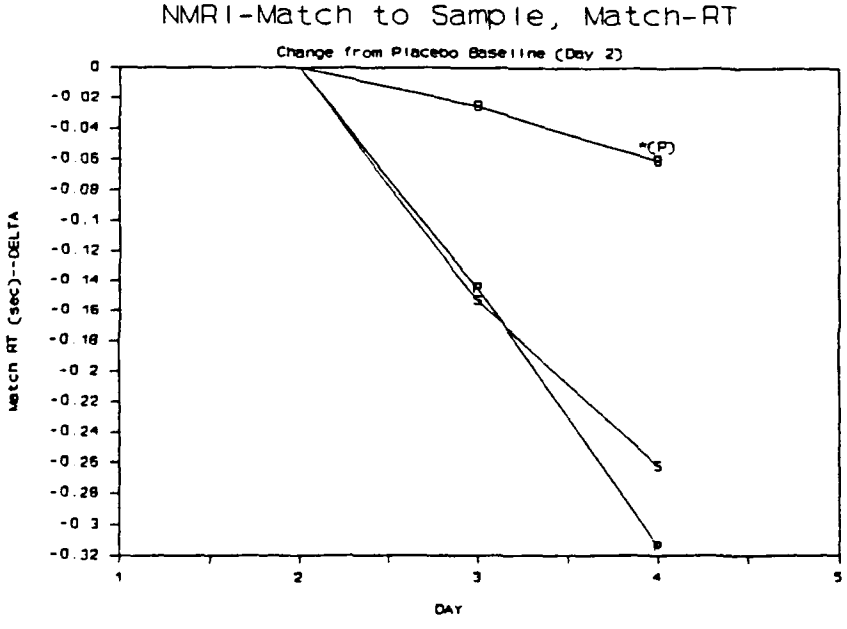


Figure 19. Day 4 delta score drug main effect for Match to Sample, RT.

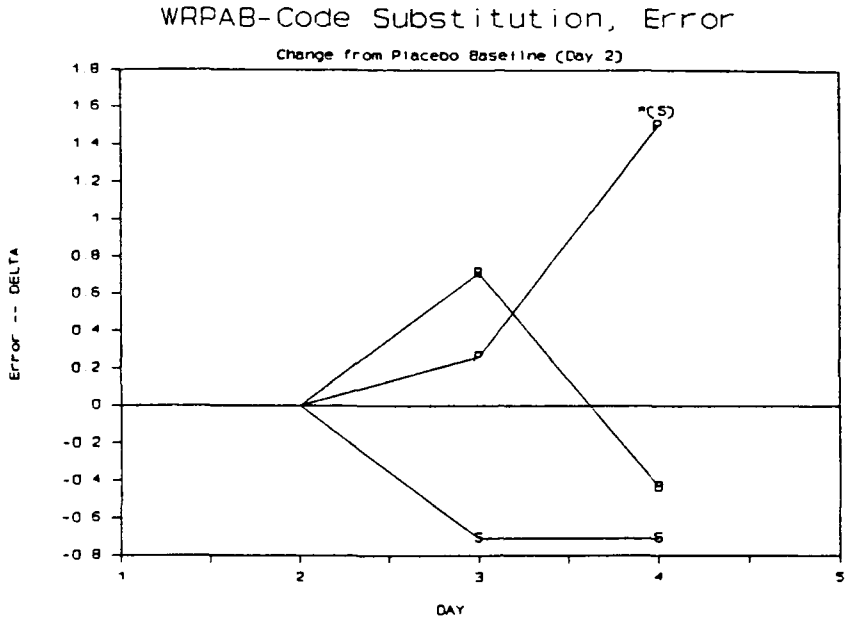


Figure 20. Day 4 delta score drug main effect for Code Substitution, Error.

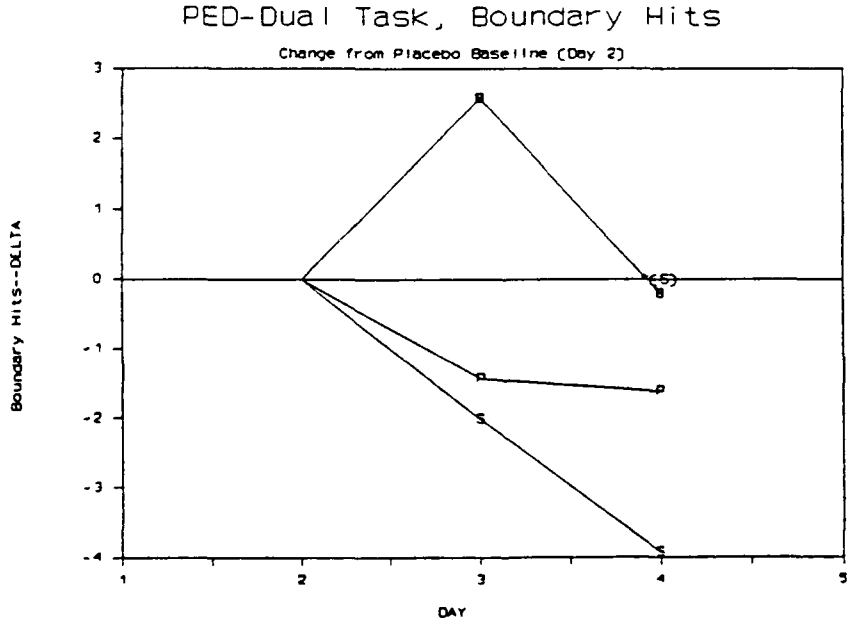


Figure 21. Day 4 delta score drug main effect for Dual Task, Boundary Hits.

Subjective Reports

The subjective reports, briefly described in Appendix B, included: MOOD II from the WRPAB (B.1.); an antihistamine side effects symptom questionnaire (B.2.); the USAF sleep survey (B.3.); and the USAF Subjective Fatigue Scale (B.4.). The results of analyses of these data appear in Table 4.

MOOD II.

Drug main effects were found for Activity $F(2,33) = 4.76$, $p = 0.02$ which showed the Benadryl group reported a higher rating than the Placebo group; and Happiness $F(2,33) = 6.57$, $p < 0.01$ which showed higher ratings for the Benadryl and Seldane groups compared to the Placebo group.

Day main effects were also found and included: Activity $F(2,66) = 5.72$, $p < 0.01$ where on Day 3 less activity was reported than on Day 4; Happiness $F(2,66) = 13.58$, $p < 0.01$ showed lower ratings on Days 2 and 3 than Day 4; Fatigue $F(2,66) = 3.43$, $p = 0.04$ showed that ratings were greater for Day 3 than Day 4; and Fear $F(2,66) = 4.92$, $p = 0.01$ showed that ratings were greater on Days 2 and 3 than on Day 4.

A test session main effect found lower Depression ratings $F(1,33) = 7.13$, $p = 0.01$, and lower Anger ratings $F(1,33) = 6.40$, $p = 0.02$ during the early morning sessions rather than the early evening sessions. A drug-by-day interaction was found for the Anger measure $F(4,66) = 2.85$, $p = 0.03$, showing lower Benadryl group ratings on Day 2 compared to the Placebo group, and on Day 4 compared to the Placebo and Seldane groups.

Antihistamine Symptom Questionnaire.

An ANOVA was conducted with the antihistamine questionnaire data. The results of comparisons for each symptom by drug, day, and session showed two drug main effects for the hunger symptom $F(2,32) = 6.81$, $p = 0.003$, and the flushed symptom $F(2,32) = 3.34$, $p = 0.05$; a day main effect for the restlessness symptom $F(2,63) = 5.55$, $p = 0.006$; and several session main effects including drowsiness $F(3,96) = 7.19$, $p = 0.0002$, fatigue $F(3,96) = 12.21$, $p = 0.0001$, hunger $F(3,96) = 12.11$, $p = 0.0001$, and sore throat $F(3,96) = 3.43$, $p = 0.02$. Three drug-by-session effects were found for the headache $F(6,96) = 2.81$, $p = 0.01$, hunger $F(6,96) = 2.62$, $p = 0.02$, and the flushed $F(6,96) = 2.70$, $p = 0.02$ symptoms.

There were three drug-by-day effects including: drowsiness $F(4,63) = 3.21$, $p = 0.01$ was rated much higher by the Benadryl group than by the Seldane group on Day 3 and shown by an asterisk in Figure 22; restlessness $F(4,63) = 2.90$, $p = 0.02$ was rated lower by the Benadryl group on Day 2 compared to Seldane and lower than the Placebo group on Day 3 as shown in Figure 23; the flushed symptom $F(4,63) = 3.84$, $p = 0.008$ was rated higher by the Placebo group than by the Benadryl and Seldane groups on Day 3.

TABLE 4. SUMMARY RESULTS OF SUBJECTIVE MEASURES ANALYSES

TEST	VARIABLE	SOURCE	p	EFFECT
MOOD II:	ACTIVITY	D	<0.01	3<4
		DR	0.02	B>P
	HAPPINESS	D	<0.01	2,3<4
		DR	<0.01	B,S>P
	DEPRESSION	TS	0.01	AM<PM
	ANGER	TS	0.02	AM<PM
		DR*D	0.03	B2<P2; B4<P4,S4
	FATIGUE	D	0.04	3>4
	FEAR	D	0.01	2,3>4
ANTIHISTAMINE QUESTIONNAIRE:				
	CUMULATIVE SUM	S	0.02	4>3,2,1
	DROWSINESS	S	<0.01	4,3>1,2
		DR*D	0.01	B3>S3
	HEADACHE	DR*S	0.01	P1>B1 S=non est.
	FATIGUE	S	<0.01	4>3,2,1
		DR*D*S	0.03	P22>B22,S22 B32>S32 B33>P33,S33 B34,P34>S34 P42>B42
	RESTLESSNESS	D	<0.01	N.S.
		DR*D	0.02	B2<S2;B3<P3
	HUNGER	DR	<0.01	S>B,P
		S	<0.01	2>1,3,4
		DR*S	0.02	B2>P2 S=non est.
	SORE THROAT	S	0.02	1>4,2,3

LEGEND: D = Day -- 2,3,4 = Tuesday, Wednesday, Thursday
DR = Drug -- P,B,S = Placebo, Benadryl, Seldane
TS = Test Session -- 1,2 = 1230 hr, 1330 hr
S = Session -- 1,2,3,4 = 0630, 1130, 1500, 2230 hr

TABLE 4. (cont.)

TEST	VARIABLE	SOURCE	p	EFFECT
ANTIHISTAMINE QUESTIONNAIRE:				
	FLUSHED	DR	0.05	P>B
		DR*D	<0.01	B3>P3>S3
		DR*S	0.02	P1>B1
				P2>B2
				P3>B3
				S=non est.
USAF SLEEP SURVEY:				
	RESTED	CHI-SQR(4)	<0.01	B4>S4
	MORE	LIKELIHOOD RATIO CHI-SQR(2)		
			0.04	P4,S4>B4
USAF FATIGUE SCALE:				
	FATIGUE	D	0.02	3>2,4
		DR*D	<0.01	B3>P3,S3; B4<S4
		TS	<0.01	S7>all;
				S10>all, except
				S7

LEGEND: D = Day -- 2,3,4 = Tuesday, Wednesday, Thursday
DR = Drug -- P,B,S = Placebo, Benadryl, Seldane
TS = Test Session -- 1,2 = 1230 hr, 1330 hr
S = Session -- 1,2,3,4 = 0630, 1130, 1500, 2230 hr

The fatigue symptom showed a drug-by-day-by-session effect $F(15,161) = 1.85$, **p** = 0.03. The significant contrasts for drug groups within day and session are shown in Figure 24 by asterisks. Note the greatest change in the Benadryl group from 3-4 to 4-1 and how it continues throughout Day 4 for the fatigue symptom.

A derived "cumulative symptom sum" variable was analyzed with the individual symptoms. The results indicated a session main effect $F(3,96) = 3.38$, **p** = 0.02. The cumuluative symptom sum was found significantly higher for the fourth session than the previous three sessions.

USAF Sleep Survey.

The sleep survey shown in Appendix B.3 included both a measure of the number of hours slept the night before and five questions concerning the quality of sleep. An ANOVA conducted with the number of hours slept revealed no differences in drug groups across days (or rather, nights). Chi-square tests were conducted with the data from the quality of sleep questions.

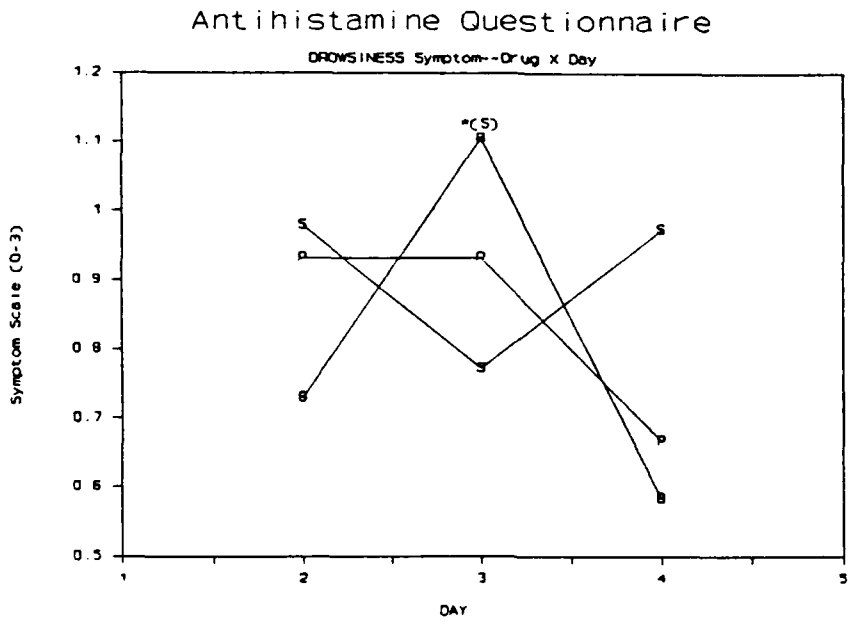


Figure 22. Drug-by-day interaction for drowsiness symptom.

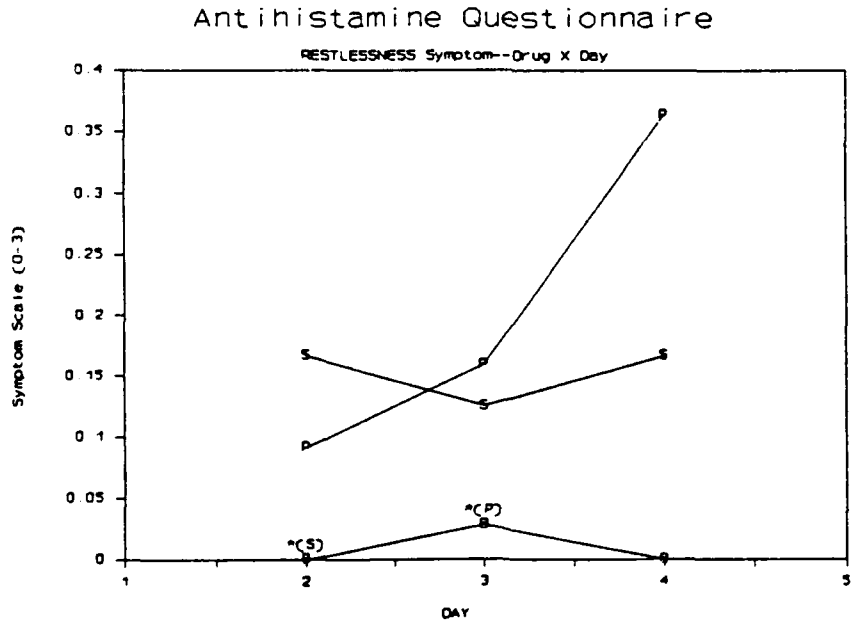


Figure 23. Drug-by-day interaction for restlessness symptom.

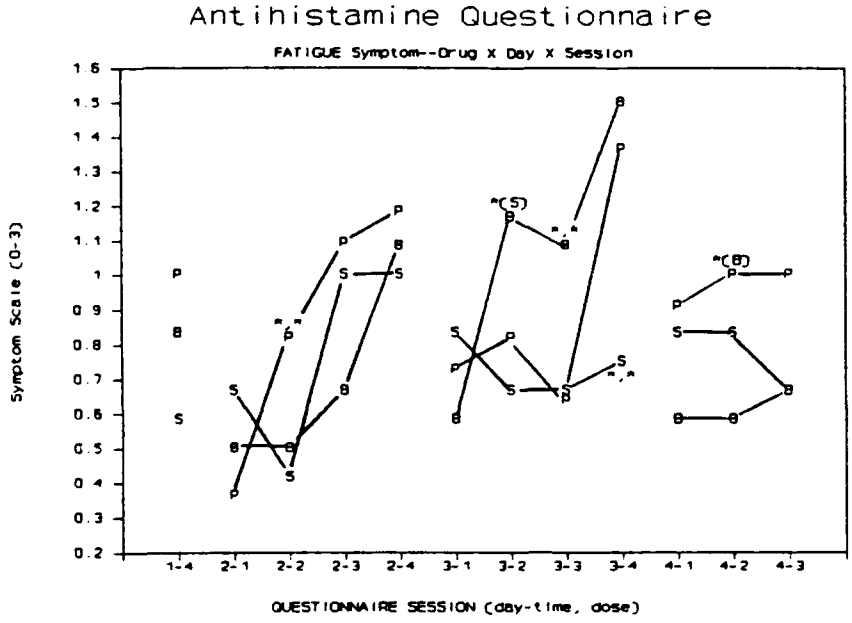


Figure 24. Drug-by-day-by-session interaction for fatigue symptom.

Sleep quality response rating frequencies, analyzed by day, showed significant chi-square results across drug group on Day 4 for the "how well rested do you feel" question, chi-square (4) = 24.16, **p** < 0.001. Seven Benadryl subjects vs. 0-Placebo and 1-Seldane subject indicated they were "well rested" Thursday morning (Day 4). Nine Placebo subjects vs. 5-Benadryl and 3-Seldane subjects indicated they were "moderately rested." Eight Seldane subjects vs. 2-Placebo and 0-Benadryl subjects indicated they were "slightly rested" on Thursday morning (Day 4). The "do you feel you could use more sleep" question showed a Likelihood Ratio chi-square(2) = 6.24, **p** = 0.04 significance indicating that the Placebo and Seldane groups desired "more sleep" compared to the Benadryl group on Day 4. Bar graphs of mean responses by drug group across days (with respect to each previous evening's sleep) show both the "well rested" question and the "more sleep" question in Figures 25 and 26.

USAF Subjective Fatigue Scale.

The USAF Subjective Fatigue Scale (Appendix B.4.) results showed a day main effect F(2,66) = 4.07, **p** = 0.02 where fatigue ratings were greater for Day 3 than for Days 2 and 4. A test session main effect was also found, F(5,165) = 12.69, **p** < 0.01, showing the post 8-test PAB rating greater than all other ratings; and the post PM-Simulation rating greater than the AM-Simulation, but less than the post 8-test PAB rating.

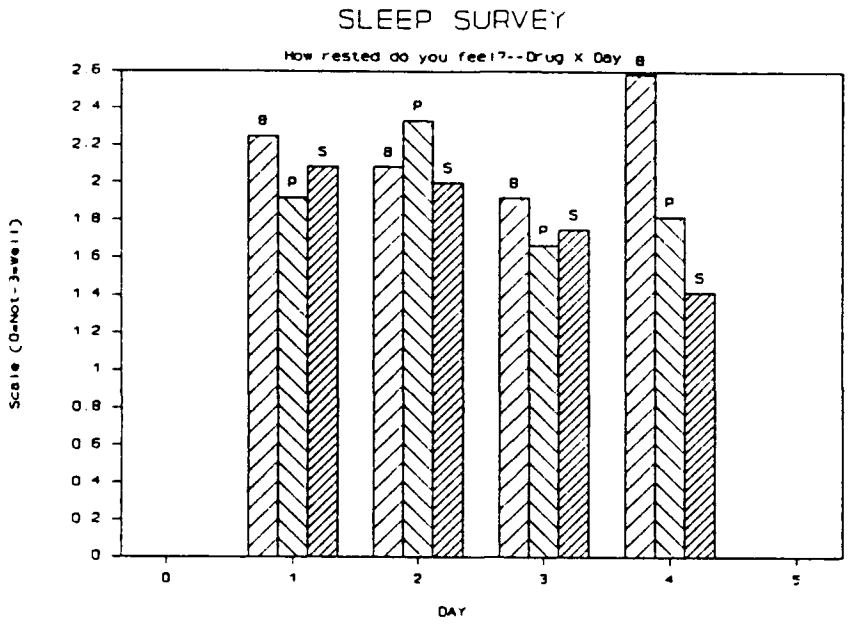


Figure 25. Drug-by-day "How well rested"--mean responses.

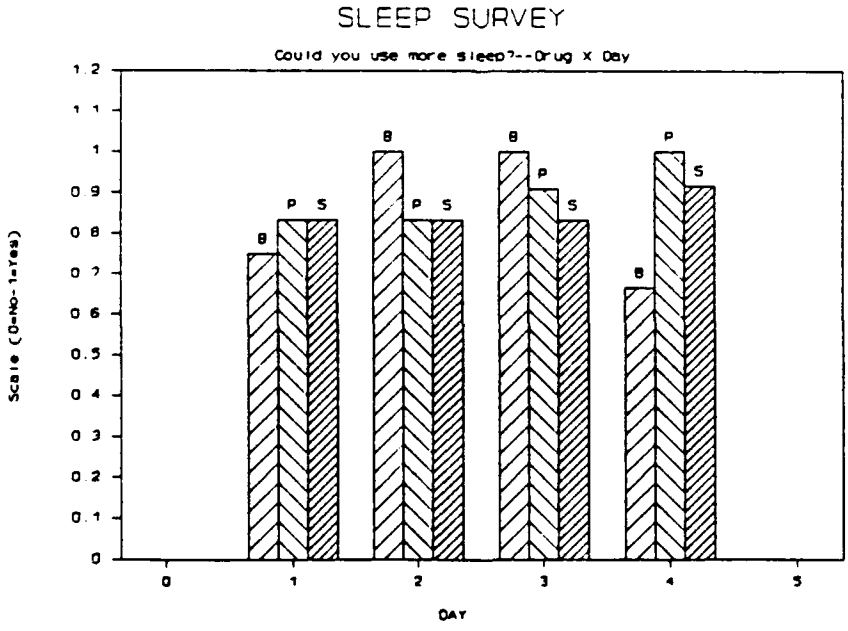


Figure 26. Drug-by-day "Could you use more sleep"--mean responses.

Mean ratings for all pre- and post-events for Days 2, 3, and 4 are shown in Figure 27. A drug-by-day interaction was also found for the fatigue scale $F(4,66) = 7.37$, $p = 0.0001$. Averaged across sessions, the Benadryl group ratings were greater on Day 3 compared to the Placebo and Seldane group ratings; and less than the Seldane group ratings on Day 4. These effects are indicated by asterisks in Figure 28.

DISCUSSION

Results of previous research with H_1 selective histamine antagonists with nonsedating properties have shown little or no performance degradation on simple cognitive tests. The present comparative study was conducted to assess the effects of two antihistamine conditions and a placebo condition on simple and complex cognitive and psychomotor task performance. One objective was to find supporting evidence that the Seldane condition produced no performance impairment. To assess a "no performance effect" hypothesis for the Seldane condition, we included a centrally active H_1 antihistamine condition for comparison in our experimental design. Benadryl was selected for this condition because of its known negative side effects associated with drowsiness. We reasoned that we could provide the evidence necessary to support our "no performance effect" hypothesis by identifying the tests or measures displaying performance degradation with the Benadryl condition and not with the Seldane and Placebo conditions. Since the study was not a clinical assessment of the efficacy of either antihistamine, our subjects were asymptomatic with respect to the usual therapeutic use for antihistamines (e.g., seasonal allergies).

From our research design, we anticipated the following: (1) no performance differences between conditions on Day 2 (during which all groups received placebo); (2) Benadryl group differences (performance impairment) during the remaining 2 days; (3) no differences between the Seldane and Placebo conditions during the 3 days; and (4) a progressive fatigue-related decrement in performance across the three days for all groups.

In our research design, significant drug-by-day interactions with appropriate post hoc contrasts were predicted to best assess our hypotheses. In the event of unanticipated group differences on Day 2, however, a drug main effect analysis with delta scores would be conducted separately for Days 3 and 4.

Our initial 3-day analysis did show differences between groups on Day 2, the single-blind placebo baseline day. Therefore, the delta-score analyses were performed with the data for Days 3 and 4, separately. Convincing evidence to support a drug effect hypothesis on Day 3 was found. Eight variables showed significant differences. In seven of the eight measures, the Benadryl group showed significant task impairment compared to the Seldane and/or Placebo conditions on Day 3.

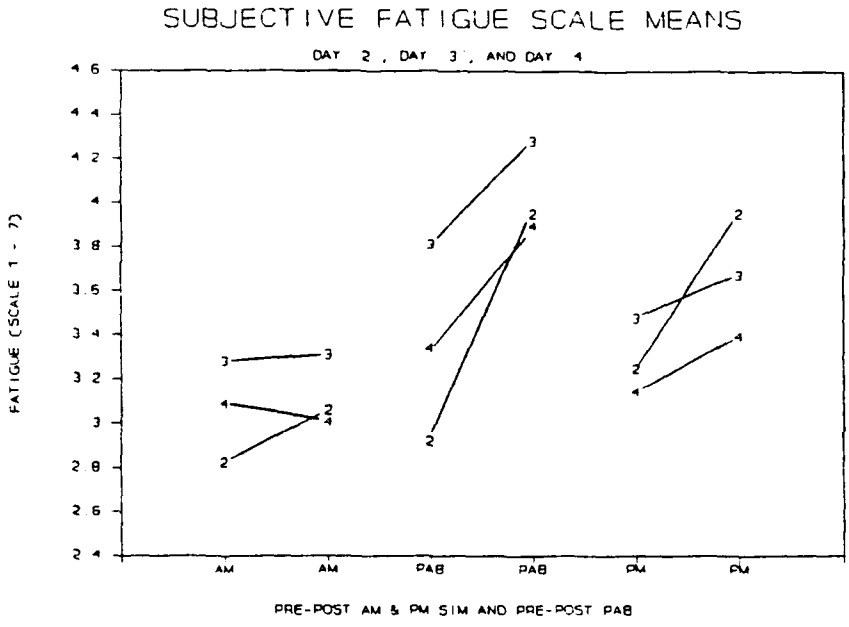


Figure 27. Day-by-session subjective fatigue scale means.

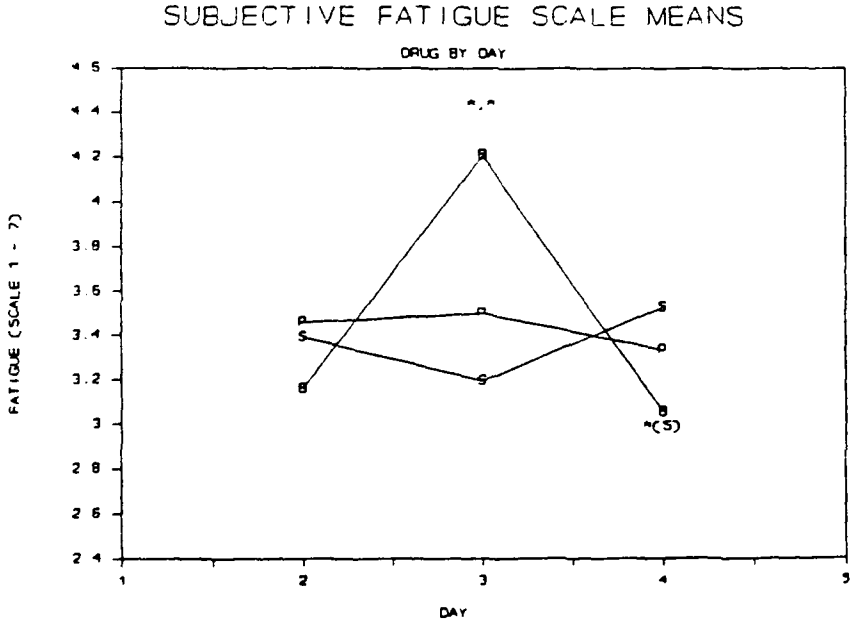


Figure 28. Drug-by-day subjective fatigue scale means.

The eighth variable, a derived throughput measure of the Dual Task, showed improvement from Day 2 with the Placebo group performing statistically better than the Seldane and Benadryl groups. Except for this eighth measure, a powerful and consistent trend of performance decrement is seen in the Day 3 data for the Benadryl group (refer to Figures 7-14). Since, in seven of the eight measures, the Seldane and Placebo groups did not differ significantly, and one or both differed significantly from the Benadryl group, we believe the results support the "no performance effect" hypothesis proposed for the Seldane condition.

Additional statistical evidence for a Benadryl group effect was found in the subjective measures analyses. The Antihistamine Symptom Questionnaire data revealed that drowsiness and fatigue (refer to Figures 22 and 24), were reported at higher levels on Day 3 by the Benadryl group compared to the Seldane and/or Placebo groups. The USAF Subjective Fatigue Scale also showed a characteristic increase in symptom level on Day 3 for the Benadryl group compared to the Seldane and Placebo groups, which were not different from one another (see Figure 28).

The delta-score data for Day 4 represented the change in performance from Day 2-placebo baseline and showed evidence that degraded performance continued for the Benadryl group compared to the Seldane and/or Placebo groups. We anticipated continued differences for the Benadryl condition.

Four variables did show drug effects on Day 4. The Numbers and Words' first "word" solution measure, showed a continued performance degradation by the Benadryl group compared to that for the Seldane and Placebo groups (seen in Figure 10). Increased Match RT and Boundary hits was further evidence of Benadryl group impairment compared to the Placebo and/or Seldane groups (Figures 19 and 21). The error measure for the Code Substitution test showed performance degradation on Day 4 but for the Placebo group compared to the Seldane group (Figure 20).

Although fewer predicted performance effects were found to occur during Day 4, the data supported the notion that cognitive abilities continued to be affected by the Benadryl condition and not by the Placebo and/or Seldane conditions.

The subjective data for Day 4 revealed results that we had not anticipated. The subjective measures showed evidence that the Benadryl group may have had a better night's rest Wednesday evening compared to the Seldane and Placebo groups. This result should not have surprised us since diphenhydramine is found in some sleep-aid preparations. It may also help explain an improvement trend seen in many of the figures for the Benadryl group on Day 4 compared to Day 3 (see Figures 7-14). In the figures showing the Day 3 Benadryl effect, performance appears to improve dramatically on Day 4 for the Benadryl condition.

Other subjective data showed that WDs in the Benadryl group reported less fatigue during Day 4. A significant chi-square analysis showed Day 4 differences between drug groups for the "how well rested do you feel?" question as well as the "could you use more sleep?" question. Figures 25 and 26 display means for the two quality of sleep questions and show a clear separation of ratings by the Benadryl group compared to the other two groups on Day 4. Another statistical illustration of this trend is seen in Figure 24. Notice the gross reduction in subjective fatigue on Thursday compared to late Wednesday (see sessions 4-1, 4-2, and 4-3 compared to 3-4 in Figure 24). Additionally, Figure 28 shows reduced fatigue ratings by the Benadryl group compared to the Seldane group measured by the USAF Subjective Fatigue Scale on Day 4. Perhaps one final indication was found with the MOOD II Scale which showed lower Anger-factor scores reported by the Benadryl group on Day 4 compared to either the Seldane or Placebo groups.

After considering the subjective data trends of Day 4, we believe that the Benadryl group experienced a better night's rest compared to the other two groups. Another explanation may come from the compensatory production of histamines in our asymptomatic subjects during Day 3 in response to ingesting antihistamines[1]. Although such histamine production is also occurring in the Seldane group, the affective behavioral change might be more pronounced with a centrally active H_1 type antihistamine.

Very little evidence of cumulative fatigue was seen in the data. This result was a surprise. We reasoned that fatigue would interact with the drug conditions and manifest itself in considerably degraded performance during Day 4. By design, their duty schedules occupied all free time. The WDs were not allowed to rest at any time during the wakeful portion of the three experimental days nor during the first day of training. Each day was long and involved, but little evidence was found to support a cumulative fatigue effect.

Another potential source of interest to us was the drug-by-test session interaction. We reasoned that a behavioral assessment of potential peak plasma effects could be determined by a drug-by-test session analysis for Days 3 and 4. Four variables showed significant interactions; interpretation, however, was difficult and inconclusive.

CONCLUSIONS

The results of our assessment of the effects of Seldane and Benadryl on cognitive and psychomotor task performance were consistent with previous research. Over the course of our

---

[1]Personal communication with Dr. Jonathan French, a behavioral pharmacologist, Armstrong Laboratory, CFTO, Brooks AFB, TX.

experiment we found that Benadryl produced performance task deficits including: (1) increased response time to simple and complex spatial pattern comparisons, (2) reduced recognition accuracy of "word" patterns embedded in visual noise, (3) increased response times and reduced accuracy of composite scores for two complex cognitive tasks, (4) reduced recognition accuracy of numeric stimuli embedded in auditory letter "noise", (5) increased tracking error and reduced overall tracking control, and (6) increased response times of visual pattern matching.

Seldane, on the other hand, was not appreciably different from placebo in its effect on task performance, but was different from the Benadryl-produced effects listed above. We feel justified in concluding that Seldane did not produce simple or complex task performance deficit under the conditions studied in this research. These results, in part, support awarding medical flying waivers to nonpilot aircrew who are taking Seldane under the supervision of flight surgeons.

REFERENCES

Betts, T., Markman, D., Debenham, S., Mortiboy, D. and McKevitt, T. (1984). Effects of two antihistamine drugs on actual driving performance. British Medical Journal, 288, 281-282.

Boggs, P.B. (1987). Clinical Experience with Terfenadine Worldwide Trials. Proceedings of Current Pharmacotherapy for Allergic Rhinitis and Urticaria. The Journal of Respiratory Disease, 7, 36-46.

Clarke, C.H., and Nicholson, A.N. (1978). Performance studies with antihistamines. British Journal of Clinical Pharmacology, 6, 31-35.

Eddy, D.E., Dalrymple, M.A., and Schiflett, S.G. Comparative Effects of Antihistamines on Aircrew Mission Effectiveness Under Sustained Operations. (Technical Report pending review) Armstrong Laboratory, Brooks AFB, Texas.

Englund, E.C., Reeves, R.L., Shingledecker, C.A., Thorne, D.R., Wilson, K.P., and Hegge, F.W. (1985). Unified Tri-Service Cognitive Performance Assessment Battery (UTC-PAB) I: Design and Specification of the Battery, JWGD3 MILPERF Report No. 85-1, U.S. Army Research and Development Command, Fort Detrick, Maryland.

Fink, M., and Irwin, P. (1979). CNS effects of the antihistamines diphenhydramine and terfenadine (RMI 9918). Pharmakopsychiatrist, 12, 35-44.

Kulshrestha, V.K., Gupta, P.P., Turner, P. and Wadsworth, J. (1978). Some clinical pharmacological studies with terfenadine, a new antihistamine drug. British Journal of Clinical Pharmacology, 6, 25-29.

Nicholson, A.N., Smith, P.A., and Spencer, M.B. (1982). Antihistamines and visual function: Studies on dynamic acuity and the pupillary response to light. British Journal of Clinical Pharmacology, 14, 683-690.

Nicholson, A.N., and Stone, B.M., (1986). Antihistamines: Impaired performance and the tendency to sleep. European Journal of Clinical Pharmacology, 30, 27-32.

Perez, W.A., Masline, P.J., Ramsey, E.G., and Urban, K.E. (1987). Unified tri-services cognitive performance assessment battery: Review and methodology. Technical Report AAMRL-TR-87-007, Armstrong Aerospace Medical Research Laboratory, Wright-Patterson AFB, Ohio.

Physicians' Desk Reference (1989). Downd AL (ed.), 43rd Edition, Medical Economics Company, Inc., Oradell, N.J.

Reeves, D.L., Thorne, D.R., Winter, S.L., and Hegge, F.W. (1989). The Unified Tri-service Cognitive Performance Assessment Battery (UTC-PAB). II. Hardware/Software Design and Specifications. JWGD3 MILPERF REPORT NO. 89-1, NAS, Pensacola, FL; WRAIR, Washington, DC.

Samet, M.G., Marshall-Mies, J.C., and Albarian, G. (1987). Expanded complex cognitive assessment battery (CCAB): Final test administrator user guide. AAC-UM-33212, Analytical Assessments Center, CA: Los Angeles. Deliverable under Contract MDA903-84-C-0449 to U.S. Army Research Institute, VA: Alexandria.

Shingledecker, C.A., (1984). A task battery for applied human performance assessment research. Technical Report No. AFAMRL-TR-84-071, Air Force Aerospace Medical Research Laboratories, Wright-Patterson AFB, Ohio.

Sorkin, E.M., and Heel, R.C., (1985). Terfenadine: A review of its pharmacodynamic properties and therapeutic efficacy. International Journal of Current Therapeutics and Applied Pharmacology Reviews, ADIS Press International, Inc. Newtown, PA.

Spector, S.L. (1987). The pharmacology of antihistamines. Proceedings of Current Pharmacotherapy for Allergic Rhinitis and Urticaria. The Journal of Respiratory Diseases, 7, 24-28.

Systems Research Laboratories (1987). Combined Memory Search-Tracking Task (PED) Operators Manual, Version 2.1. SRL, Chesapeake Bay Office, California, Maryland.

Thomas, J.R. and Schrot, J. (1988). Naval Medical Research Institute Performance Assessment Battery--Documentation. NMRI 88-7, Naval Medical Research and Development Command, Bethesda, Maryland.

Thorne, D.R., Genser, S.G., Sing, H.C., and Hegge, F.W. (1985). The Walter Reed Performance Assessment Battery. Neurobehavioral Toxicology and Teratology, 7(4), 415-418.

APPENDIX A

Cognitive and Psychomotor Tests
of the 8-test PAB

The following paragraphs list the 8 tests and their various measures. These tests were chosen because they are similar to some of the tasks performed by Weapons Directors and embedded in the AWACS simulation scenarios, and because they have a history of sensitivity to both fatigue and antihistamines.

A.1. Matching to Sample. The subject is forced to make a choice between the left or right stimulus matrix as the match for the previous sample matrix. The data collected for each trial were the time of the subject's response to the sample (memorization time), time of response to the left or right choice, and whether the answer was correct or incorrect.

A.2. Code Substitution. The subject selects a number that is the code for the probe letter presented. The data include the number of errors, the mean response time (RT), and mean correct RT. Other data stored were the subject number, session number, and number of help requests. If the help key was pressed, the subject was given the codes to look through for the correct answer.

A.3. Pattern Comparison. The subject indicates whether or not an asterisk pattern is the same as or different from the immediately preceding asterisk pattern. The data include the number of errors, the mean RT, and the mean correct RT. Other data stored were the subject number and session number.

A.4. Logical Reasoning. The subject indicates whether or not the relationships of two letters match the meaning of a short statement. The data include the number of errors, the mean RT, and the mean correct RT. Other data stored were the subject number and session number.

A.5. Mark Numbers. The subject marks, by pressing the space bar, numbers meeting defined criteria. In a secondary interruption task, the subject marks special flashing numbers. The data include the total time for completing the marking, the number of hits, the mean time per hit, a composite score, whether or not the correct flashing number was hit, and the RT. Elaboration of each scoring computation can be found in the CCAB manual (1/30/88).

A.6. Numbers and Words. The subject responds to the keys 1, 2, and 3 to record the value of the previously displayed number currently on the screen. A secondary task is to identify a three-character nonsense syllable (word) emerging from background clutter. Six alternatives are identified by the letters A - F. The subject keys in the letter corresponding to the syllable. The data include the percent of good hits, the percent of bad hits, the percent of misses, the signal detection theory (SDT) index, the time adjusted SDT, mean time, standard deviation of time, the total word identification time, and a composite score. Again, elaboration of these scoring computations can be found in the CCAB manual (1/30/88).

A.7. Dual Task. The subject attempts to control an unstable cursor with a joystick by keeping it aligned on a horizontal plane over a central point while pressing one of two buttons to indicate membership of a probe letter to a previously displayed set of 4-letters. Data included the root mean square (RMS) offset from the central point, the number of boundary hits, the mean correct RT to the probes, the correct RT standard deviation, and the number of correct probes. Other data stored includes the date, session number, experimenter, subject number, memory set size, and trial number.

A.8. Dichotic Listening. Subjects hear different alphanumeric sequences in each earphone. At the beginning of each trial, a cue signaled which ear-channel to attend. The subject's response was to key in on the row-numbers, each number heard in the attended channel and to ignore/filter the alphanumerics of the other ear-channel and the letters of the attended ear-channel. There were 2 alphanumeric sequences per trial with 12 trials. The data are the total incorrect (or missed) in the first sequence regardless of sequence, total incorrect (or missed) in the second sequence regardless of sequence, total incorrect (or missed) in the first sequence counting sequence, and total incorrect (or missed) in the second sequence counting sequence. Other data stored were the subject number, day, month, date of year, time, session number, and total number of responses.

APPENDIX B

Subjective Surveys, Scales, and Questionnaires

B.1. MOOD II Survey. The Mood II survey is modeled after the Profile of Mood States (POMS), but has only 36 key items instead of 65. The subject's response is the level, 1 to 3, of agreement with each item. The items factor into six indices of mood including: Activity, Happiness, Depression, Anger, Fatigue, and Fear. The raw data were the sum of the values given by the subject on each scale. Since the total number of items differ in each subcategory, the scores require conversion to percent of maximum possible. Other data stored were the subject number, the session number, and the number of items completed.

B.2. Antihistamine Symptom Questionnaire. The antihistamine symptom questionnaire was developed for our study by KRUG Life Sciences (San Antonio Division) personnel by identifying the potential symptoms and side effects of each antihistamine and a lactose intolerance reaction. These "symptoms" were then listed with a four-point scale indicating a level of interference from 0 (no symptom), 1 (symptom present but not troublesome), 2 (symptom somewhat troublesome but not interfering with normal activities), and 3 (symptom sufficiently troublesome to interfere with normal activities).

B.3. USAF Sleep Survey. The Sleep Survey (AFSC Form 3218, USAFSAM Form 154, Sep 76) lists 4 questions, the first of which displays a time scale for the individual to mark out each successive half-hour interval block "that you slept yesterday and today." The second question asks "How much trouble did you have going to sleep last night?"--none; slight; moderate; considerable. Question three asks "How well rested do you feel?"--not at all; slightly rested; moderately rested; well rested. Question four asks "Do you feel like you could have used some more sleep?"--yes; no. Two additional questions were added to the back of the form. Question five asks "Last night's sleep pattern:"--restless; moderate; deep. Question 6 asks "Awakenings:"--none; infrequent; frequent.

B.4. USAF Subjective Fatigue Scale. The USAF Subjective Fatigue Scale (from the Crew Status Survey; AFSC Form 3243, Jun 85) simply asks the individual to circle the number of the statement which describes how you feel **right now**, and lists seven statements: 1) Fully alert; wide awake; extremely peppy, 2) very lively; responsive, but not at peak, 3) Okay; somewhat fresh, 4) A little tired; less than fresh, 5) Moderately tired; let down, 6) Extremely tired; very difficult to concentrate, and 7) Completely exhausted; unable to function effectively; ready to drop.